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Biomimetic nanosystems for pancreatic cancer therapy: A review☆

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ABSTRACT

Pancreatic cancer (PC) is a highly lethal and aggressive malignancy, currently one of the leading causes of cancer-related deaths worldwide, in both women and men. PC is highly resistant to standard chemotherapy (CT) because its immunosuppressive and hypoxic tumor microenvironment and a dense desmoplastic stroma compartment extensively limit drug accessibility and perfusion. Although CT is one of the main therapeutic strategies for PC management contributing to tumor eradication through a cytotoxic effect, CT is associated with a poor pharmacokinetic profile and provokes deleterious systemic toxicity. This low efficacy-poor safety scenario urgently calls for innovative and highly specific therapeutic strategies to counteract this urgent clinical challenge. Nanotechnology-based precision materials for cancer may help improve drug stability and minimize the systemic cytotoxic effects by increasing drug tumor accumulation and also enabling controlled release, but several drawbacks still persist, such as the poor targeting efficiency. In the last few years increased attention has been paid to bioinspired nanosystems that can mimic either partially or totally biological systems, including lipid layers as suitable stealth coatings resembling the composition of cell membranes, lipoprotein- and blood protein-based nanosystems, and cell membrane-derived systems, such as extracellular vesicles, cell membrane nanovesicles and cell membrane-coated nanosystems, which display intrinsic cancer-targeting abilities, enhanced biocompatibility, decreased immunogenicity, and prolonged blood circulation profile. This review covers the recent breakthroughs on advanced biomimetic PC-targeted nanosystems, focusing on their design, properties and applications as innovative, multifunctional and versatile tools paving the way to improved PC diagnosis and treatment.

1. Introduction

1.1. Pancreatic cancer: Overview

Cancer ranks among the deadliest diseases, associated with significant burden, often fatal prognosis, and huge clinical challenge [1]. Cancer management has substantially improved mainly on enhanced cancer diagnostics and therapeutics and personalized therapy, resulting in extended survival rates and decreased mortality worldwide. In this regard, Pancreatic cancer (PC) is one of the most challenging tumors, characterized as a strongly aggressive disease with dismal prognosis and a poor 5-year survival rate [2]. Apart from the extremely late diagnosis, the approved therapeutics have limited applications and efficiency, which dampens survival of patients diagnosed with PC [3,4]. Moreover, the existence of appropriate biomarkers of disease is currently unavailable and widely sought after [5]. The most common and deadly PC subtype arises from the exocrine portion of the pancreas and is an adenocarcinoma – Pancreatic Ductal Adenocarcinoma – that has well-defined mutational landscape including mutations in Kirsten rat sarcoma viral oncogene homologue (KRAS), TP53, CDKN2A and SMAD4

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genes which have been implicated as drivers in PC development [6,7]. PC is a multifactorial and complex disease with insufficiently attributed causes, although some risk factors have been pinpointed including obesity, smoking, high-fat diet, and alcohol consumption, which may interfere in PC initiation and progression [8]. Familiar history and genetical landscape also play a role.

PC is a highly desmoplastic cancer type with unmet challenges. In one side, PC cells constitute the primary entities regarding PC progression and metastasis and are typically highly resistant to instituted CT, as they develop mechanisms to decrease sensitivity or inactivate CT drugs. PC cells also display poor immunogenicity and are not able to trigger efficacious immune responses either by poor quality or low quantity of antigens, or by upregulation of immunosuppressive molecules which inhibit immune cell-mediated killing. Additionally, the maintenance of a PC stem cell pool is suggested to help tumor spread, therapy resistance and tumor relapse [9–11]. On the other hand, PC is surrounded by a dense, fibrotic and aberrant stroma compartment – composed mainly of cancer-associated fibroblasts (CAFs), involved in extracellular matrix (ECM) production and crosstalk mechanisms that instigate PC spread and metastasis, and their more quiescent relatives – pancreatic stellate cells (PSCs), which also contribute to ECM production in the activated state. Although CAFs have been pointed out as key mediators of PC progression through ECM production, growth factors and other immunomodulatory signals, recent studies have shown the heterogeneity of their origin and function, as different CAF subtypes may co-exist and thus imparting different outcomes [12–15]. For instance, myofibroblastic CAFs (myCAFs) are often considered tumor restraining on account of their immunoactivation properties, while antigen-presenting CAFs (apCAFs) and inflammatory CAFs (iCAFs) typically engage in immunosuppression mechanisms further driving PC growth and metastasis [16]. The immune cell composition is scarce and limited to immunosuppressive phenotypes, such as regulatory T cells (T_{regs}), myeloid-derived suppressor cells (MDSCs) and pro-tumorigenic M2 macrophages (anti-inflammatory). T_{regs} suppress immune responses through cytokine production and cytotoxic T cell inhibition, while MDSCs engage in T cell inactivation and M2 macrophages are associated to immunosuppression and poor prognosis [17,18]. Endothelial cells integrate the vasculature rendering oxygen and nutrients to cancer cells and their surroundings and nerve cells are present during perineural invasion (PNI) of PC, and nerve-PC crosstalk is known to foster PC progression and invasion [19,20] (Fig. 1. A, B).

The stroma compartment consists of a physical barrierof compacted CAFs overly producing ECM components - collagen, fibronectin, matrix metalloproteinases - which increases drastically the compactness and density of the stroma compartment [19,21]. Because of this, drugs and delivery systems have difficulty penetrating and transversing this stroma barrier. This also leads to high interstitial pressure, which limits even more drug diffusion and penetration of drug delivery systems. Secondly, PC stroma and tumor microenvironment (TME) are highly immunosuppressive [19], as few immune cells are able to penetrate the physical barrier and interact with tumor cells; effector immune cells are not recruited in sufficient amounts; and immune evasion mechanisms take place mediating immune cell inactivation [22]. Moreover, the hypoxic nature of PC is characterized by hypovascularization which maximizes the previously described hurdles. Other modifications verified in PC cells and TME with implications in disease progression also include metabolic abnormalities [23], PC-stroma-extracellular vesicle crosstalk [24] and the role of gut and intratumoral microbiota [25]. Additionally, stroma-associated stiffness is linked to ECM overproduction and is known to drive cancer progression and confer resistance to common chemotherapeutic drugs [26,27] (Fig. 1. A, B).

1.2. Pancreatic cancer: Therapeutics and challenges

PC is a very complex disease, and its therapeutic regimen depends on cancer staging [28,29]. CT, along with radiotherapy and surgery,

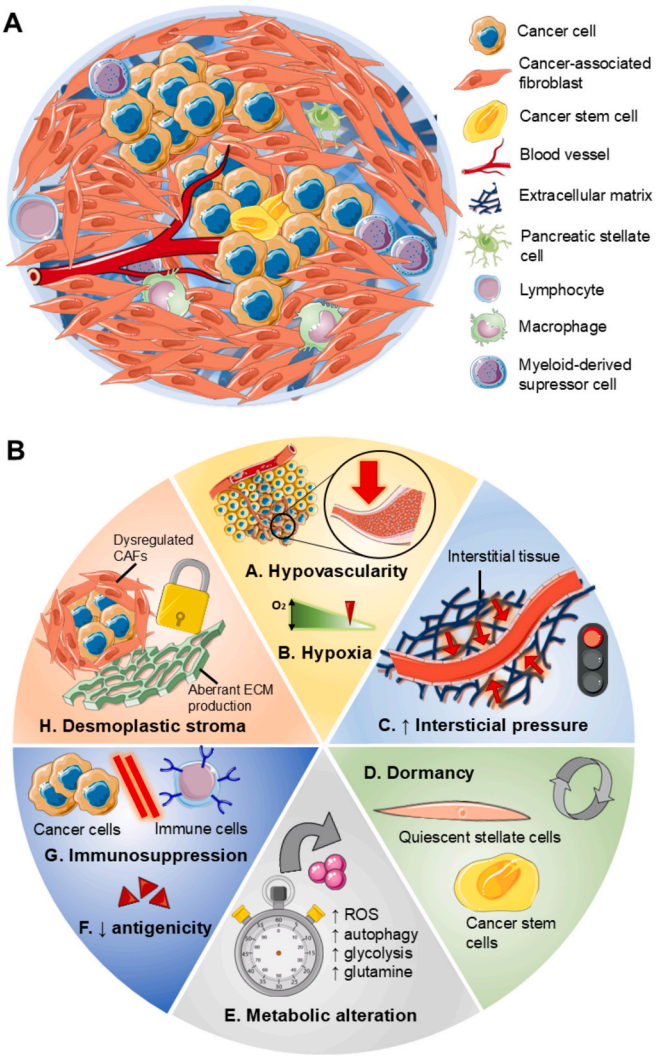

Fig. 1. (A) Schematic illustration of pancreatic cancer (PC) tumor microenvironment (TME). PC cells are surrounded by a dense layer of cancer-associated fibroblasts (CAFs) and abundant extracellular matrix (ECM) composed of collagen, fibronectin and enriched in matrix metalloproteinases. A pool of cancer stem cells (CSC) resides in the primary tumor and is responsible for arising resistance to chemotherapeutic drugs and tumor relapse. The primary tumor is supplied by small caliber blood vessels which are often of low number and collapse on account of the dense stroma and overproduced matrix content. TME further contains myofibroblast-like cells known as pancreatic stellate cells (PSCs) that secrete ECM and related enzymes. Due to the immune-excluded nature of PC and the hypoxic dense TME, few immune cells can infiltrate and locate next to PC cells, including cytotoxic T lymphocytes and macrophages. Immune suppressor cells such as myeloid-derived stem cells (MDSCs) and regulatory T cells (T_{regs}) further amplify immunosuppression hindering normal eradication of PC cells and drive PC progression. (B) Major hallmarks of PC TME include A – hypovascularity associated with B – hypoxic TME, C – dense and desmoplastic stroma compartment leading to vascular compression, high interstitial pressure and hindered penetration of drugs and immune cells in the TME, D – presence of PSCs and CSCs which are key players in PC progression and relapse. Additionally, E – Metabolic alteration consists of maintenance of high demand of glycolytic pathway for energy production, production of high levels of ROS, and dependence on other nutrient sources such as lipid and glutamine metabolism. PC is also associated with decreased mutation burden and antigenicity, F, and G- immunosuppressed TME, further accentuated by aberrant ECM production and CAF dysregulation leading to a stroma barrier – H.

represents one of the major therapeutic approaches for cancer cells eradication [28,29]. CT is one of the main pillars of PC therapy, and gemcitabine (GEM) solution for injection, Gemzar®, alone or in combination regimen with albumin-bound paclitaxel (PTX) (Abraxane®) is often employed with limited clinical efficacy [30]. FOLFIRINOX® is used in advanced PC stage and consists of a combination of several anticancer drugs, namely folinic acid, 5-fluorouracil (5-FU), irinotecan (IRT) and oxaliplatin (OXA) and remains as of now the golden standard in PC therapeutics. Standard CT has remained almost unchanged in the last 20 years [3] and is strongly associated with systemic toxicity and cancer multidrug resistance (MDR) emergence [4] due to poor cancer tissue biodistribution and accelerated drug degradation and clearance [31]. To improve the pharmacokinetic profile and stability of CT drugs, prodrug derivatives have been explored [32]. In the case of GEM, the synthesis of a prodrug helps by 1) reducing clearance and metabolic degradation by cytidine deaminase [33], 2) enabling slow GEM release profile, under physiological stimuli, and 3) improving tumor biodistribution and cell uptake [34,35]. Several small molecular weight prodrugs of GEM have been synthesized thus far and showed more suitable pharmacokinetic properties and enhanced anticancer efficiency [34,36]. Coupling GEM to polyethylene glycol (PEG), assembling PEGylated GEM, allows improving GEM circulation half-life, demonstrating the interest of developing prodrugs with hydrophilic polymers [37].

Targeted therapies explored to tackle PC are receiving increasing attention as a tool to improve targeting specificity and treatment efficacy by targeting genes associated with disease initiation, progression and metastasis [38]. Despite the huge promise, targeted therapies face challenges in PC context due to the undruggable aspects of some molecular targets, such as KRAS mutated gene, the complexity of the implicated molecular pathways, and lack of activity or even selectivity [39]. Some recent studies involving targeted therapies include development of anti-KRAS monoclonal antibodies [40], bispecific antibodies [41] and fusion proteins [42]. Antibody-drug conjugates can also help leveraging efficacy of the treatment by improving CT delivery to PC cells by employing targeting antibodies [43,44].

Other interesting strategy for PC therapy is nucleic acid therapy, in which DNA (plasmid DNA - pDNA, clustered regularly interspaced palindromic repeats (CRISPR)-associated protein 9, CRISPR/Cas9) and RNA (small interfering RNA - siRNA, micro RNA - miRNA, messenger RNA) are delivered to cells for gene silencing (small interfering RNA - siRNA, microRNA - miRNA) or aimed at protein expression (plasmid DNA - pDNA, messenger RNA - mRNA). In most cases, the necessity of a suitable carrier is required, as delivery of nucleotide-based molecules is associated with several hurdles including chemical instability, immunogenicity, susceptibility to enzymatic degradation and marked hydrophilic properties. Hence, molecule modification through chemical conjugation of stabilizing and/or targeting moieties [45], together with encapsulation in nanosystems, constitute promising alternative ways to efficiently deliver therapeutic DNA and RNA molecules [46–48].

Although less expressive, phototherapy and hyperthermic treatment have also received moderate interest in PC management, as recent studies have explored phototherapy-mediated depletion of CAFs in 3D models of disease [49], phototherapy-aided immunotherapy [50], antibody-photosensitizer conjugates for photodynamic therapy and immunogenic cell death (ICD) induction [51] and hyperthermia-mediated eradication of PC cells [52].

PC is widely regarded as a strongly immunosuppressed cancer, with a "cold" TME and is minimal responsive to immunotherapy (IT) [53,54]. Although IT mediated by immune checkpoint blockade (ICB) inhibitors (monoclonal antibodies targeting either programmed death ligand 1 - anti-PD-L1 and programmed death receptor 1 - anti-PD-1) has shown substantial efficacy in eradicating cancer cells in several malignancies, PC is currently refractory to ICB inhibitors, and several strategies have been devised to overcome poor IT response observed in this cancer. Combination strategies seem to be the best strategy to leverage IT response in PC, and is currently one of the hot topics in the field [55–57], which may be assisted by employing nanosystems [58]. Other treatments being subject of current exploration include radiofrequency ablation combination with IT for sustained and robust immune system activation [59].

Cell-based IT is another IT modality that employs cells for immunomodulation and cancer cell killing and belongs to the innovative group of cellular therapies. One example is chimeric antigen receptor (CAR)-based T cell therapy, which shows poor efficiency in solid tumor therapy, including PC. This is suggested to be due to the dense stroma physical barrier precluding infiltration of the CAR-T cells, to poor quality and quantity of antigen expression, to limited survival and functionality of T cells before reaching the tumor cells, and to the hugely immunosuppressive TME that promotes immune evasion and inhibition [60]. According to this, recent studies explored CAR-T cell therapies for PC by validating new targeting molecules and strategies [61–63] and also extending CAR concept to develop CAR-natural killer cell (CAR-NK) [64] and CAR-macrophage [65] cell therapies. Recent studies have also shown some promise in $KRAS^{G12D}$ restricted T-cell receptors that could trigger regression of PC in the context of metastatic scenario [66]. In addition to T cells, other immune cell subsets with interesting anticancer properties are also being subject of current exploration, namely NK cells [67]. Finally, cells are also being used as advanced carriers of payloads bearing targeting features and biocompatibility, such as stem cells [68] or even bacteria for lowering interstitial pressure of TME [69], as antigen carriers [70] and as probiotic systems for chemotherapy delivery and chemosensitization of PC [71].

1.3. Nanotechnologies in pancreatic cancer treatment: overview and path towards biomimetic approaches

Nanotechnologies are being widely explored in PC therapy to increase drug efficacy through site specific targeted drug delivery, promoting enhanced drug accumulation in cancer tissues and minimizing systemic adverse effects [72]. In the past, this was thought to occur passively through the enhanced permeability and retention (EPR) effect, however it is now understood that the marked cancer heterogeneity and intratumoral environment greatly compromise the ability of nanomedicines to accumulate through the EPR effect [73]. Although nanosystems can be harnessed to incorporate targeting ligands for active targeted delivery with enhanced selectivity to target cancer cells, ligand coupling processes are often laborious, expensive and complex. In order to merge structure and functionality of more than one nanosystem type, hybrid nanosystems emerge as an interesting strategy to produce lipid-polymer nanosystems, which may display enhanced biocompatibility and bioavailability as well as tunable physicochemical characteristics [74], lipid-protein nanosystems [75] or, in the case of organic-inorganic nanosystems, enhanced biocompatibility and functionalization are combined to optical, electrical or magnetic properties of inorganic nanosystems [76–79]. Despite their interesting features, these systems are more complex and may possess drawbacks verified in the nanosystems before combination.

Hence, bioinspired strategies are receiving increasing attention in which their biomimetic attributes can maximize blood circulation and drug targeting [80,81]. The majority of these nanosystems attempt to mimic cells or cell membrane components and may be of natural or synthetic origin (Fig. 2).

For example, bottom-up assembly of synthetic lipid coatings and phospholipid-mimicking structures have been applied to improve biomimetic properties and biocompatibility of nanosystems, at the same time mimicking partially the composition and structure of cell membranes. However, these nanosystems may require complex chemistry processes and are devoid of the complex surface repertoire expressed at the surface of cell membranes. Exosomes are ubiquitous cell-secreted nanovesicles which can be employed as nanosystems for targeted drug delivery to cancer cells [82]. Another approach consists of modifying

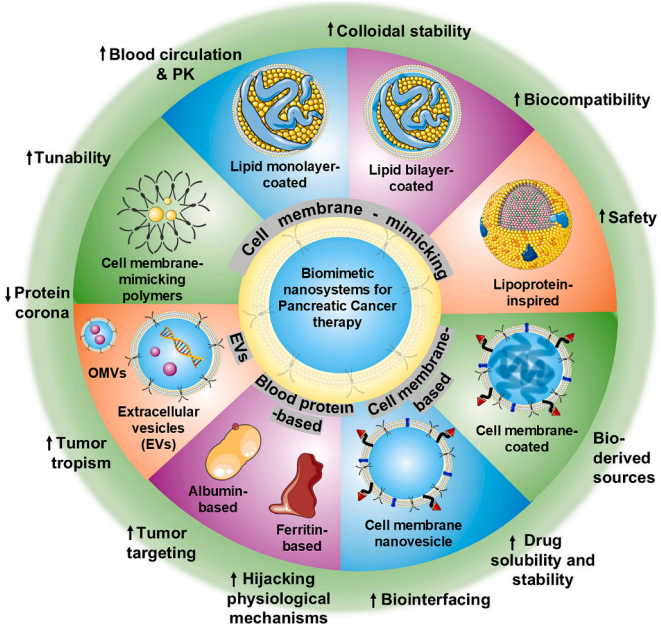

Fig. 2. Bioinspired approaches for pancreatic cancer therapy include designing nanosystems composed of cell membrane-mimicking nanostructures, namely polymer building blocks mimicking structure and function of cell membranes (cell membrane-mimicking polymers), nanosystems composed of nanoparticle (NP) cores further coated with monolayer of lipids or lipid bilayer, resembling cell membranes lipidic composition and structure, and lipoprotein-inspired nanosystems taking inspiration from naturally-occurring blood lipoproteins such as high density lipoproteins (HDLs) and low density lipoproteins (LDLs) and their physiological circuits. Additionally, nanosystems composed of cell membrane-based materials include cell membrane-coated nanosystems in which cell membranes are coated on NP cores of diverse origin, and cell membrane nanovesicles, which often result from extrusion processes to produce nanoscale water surrounding biomimetic lipid bilayers. Other biomimetic systems include extracellular vesicles (EVs) which are naturally secreted by all cells in the human body, and also protein-based nanostructures composed either of ferritin and albumin, assembling ferritin and albumin nanosystems, respectively. Outer membrane nanovesicles (OMVs) consist of spherical vesicles secreted by gram-negative bacteria with interesting biomimetic and immunostimulatory properties.

cell membranes to build cell membrane nanovesicles through a top-down approach which can later be used as biomimetic lipid bilayer-based nanostructures [83,84] or used to coat nanoparticle (NP) cores, assembling cell membrane-coated nanosystems by exploiting the inherited biofunctionalities of cell membranes extracted from source cells [85–89].

This review covers, for the first time, the design, preparation, characterization and application of biomimetic nanosystems for PC therapy, including an overview of PC pathology, current treatment options, main challenges regarding PC therapies, and details the use of nanosystems as cutting-edge tailored technologies with interesting potential for improving patient outcomes in the fight against PC. Among these nanosystems, it covers extracellular vesicles, cell membrane-mimicking nanosystems, cell membrane-coated nanosystems, cell membrane nanovesicles and blood protein-based nanosystems. The advantages and challenges of each system are also discussed, and a conclusion is provided regarding the future prospects of nanosystems as attractive platforms for PC treatment.

2. Biomimetic nanosystems for PC therapy: Preparation and characterization

Bioinspired approaches that attempt to mimic biological structures and their interactions have been shown to improve the biocompatibility, efficacy and safety of nanosystems by promoting controlled cell-surface communications. These include extracellular vesicles (EVs), synthetic cell membrane-mimicking nanosystems, cell membrane-coated nanosystems, cell membrane nanovesicles and blood protein-based nanosystems, including albumin NPs and ferritin NPs. Although few authors may consider liposomes as biomimetic nanosystems as they intrinsically pretend to mimic membrane bilayer of cells, they have been covered elsewhere [90] and special emphasis was given to lipid layers used as coating, not as isolated nanosystems for PC-targeted drug delivery.

2.1. Preparation of biomimetic nanosystems for PC therapy

The most common methods for preparation of biomimetic nanosystems for PC therapies and relevant features of each one are summarized in Table 1. EVs are mainly isolated through an ultracentrifugation protocol in which sequential centrifugation speeds allow for separation of EVs regarding their size and density [91–94] (Fig. 3. A). Other methods include density gradient centrifugation, in which sucrose is often used as increasing density medium for EV separation, size-exclusion chromatography in which EVs are isolated by size, microfluidics and PEG-mediated precipitation.

Cell membrane-mimicking polymeric nanosystems comprise polymeric building blocks with structure resemblance to membrane phospholipids and can self-assemble into drug-loaded micelles through dialysis method [95]. Other methods for preparation of drug-loaded micelles can be utilized for preparing cell membrane-mimicking polymeric nanosystems, such as thin film hydration (TFH) and solvent evaporation (Fig. 3. B). For TFH method, both drug and polymer blocks are dissolved in organic solvent, which is then evaporated and the thin film formed is then resuspended in water or another aqueous medium resulting in drug-loaded micelle nanosystems. The solvent evaporation method is the simplest method for preparing drug-loaded micelles in which drug and polymer are dissolved in organic solvent and added dropwise to an aqueous medium, under stirring, and followed by overnight evaporation of the organic solvent, and thermodynamically stable drug-loaded micelles are formed. TFH method is also frequently used for preparing synthetic lipid monolayer and lipid bilayer coated nanosystems for PC therapy. Synthetic lipid monolayer film is deposited at the surface of NP cores after TFH with prepared NP cores (Fig. 3. C) [96,97] and the synthetic lipid bilayers can be used to coat NP cores following the same procedure (Fig. 3. D), assembling liposome-coated NP cores [98,99]. Additional extrusion [100,101] or sonication [102,103] allow for size and PDI optimization of the lipid layered NP cores. Modification of liposome-like vesicles with either Apo-A1 [122] Apo-A2 [104] peptides enables the production of lipoprotein-inspired nanosystems for PC therapy (Fig. 3. E). For that, TFH method allows formation of thin film of lipids which are then reconstituted with water and Apo-A1 peptide is added to the system, followed by heat-cooling cycles [157]. A liposome emulsion method can also be used in which lipidic components are mixed and Apo-A2 peptide is added to the mixture [104]. Cell membrane-coated nanosystems consist of NP cores coated with whole cell membranes derived from source cells. The manufacture process involves extraction of cell membrane from native cells, followed by coating NP cores with previously extracted cell membrane fragments (Fig. 3. F). An intermediate step for preparing cell membrane nanovesicles is also taken to assure formation of cell membrane coating and facilitate the coating process. Cell membrane extraction comprehends a rather complex protocol in which cell membrane fragments are isolated with sufficient purity and quantity, and other intracellular components are eliminated (Table 2).

The most common cell membrane extraction method consists of hypotonic lysis of cells, followed by differential centrifugation in which nuclear content, mitochondria and other internal structures are removed, and a final membrane pellet is obtained [105,106,108,110]. This method has been developed for all cell types, including immune cells and cancer cells. Other alternatives include freeze-thaw method in

Table 1
Overview of preparation methods of biomimetic nanosystems for PC-targeted therapy. NP core preparation is not shown for clarity.

Classification	Nanosystem	Preparation strategy	Key features	Ref
Extracellular vesicles	–	Differential ultracentrifugation	• Versatility • Scalability • Efficiency	[91–94]
Cell membrane-mimicking	Cell membrane mimicking polymers	Dialysis	• High purity • Simplicity • Mild conditions	[95]
	Lipid monolayer-coated Lipid bilayer-coated	Thin film hydration	• Simplicity • Efficiency • Controllable • Time-amenable	[96,97] [98,99]
		Thin film hydration + extrusion	• Uniformity of particle size • Reproducible • Scalability	[100,101]
		Thin film hydration + sonication	• Uniformity particle size • Time-amenable	[102,103]
	Lipoprotein-inspired	Thin film hydration	• Efficiency • Controllable	[157]
		Emulsion	• Simplicity • Time-amenable	[104]
Cell membrane-based	Cell membrane-coated		• Avoids temperature-related damage	[105–107]
		Co-extrusion with membrane fragments	• Scalability • High reproducibility • Uniformity of particle size • Controlled membrane coating around NP cores	
		Sonication with membrane fragments	• Time-amenable • Simplicity • Controlled membrane coating around NP cores	[108,109]
		Co-extrusion with membrane NVs	• Avoids temperature-related damage • High reproducibility • Scalability • Uniformity of particle size • Favors incorporation of NP core in pre-formed membrane NVs	[110,111]
		Sonication with membrane NVs	• Time-amenable • Simplicity • Favors incorporation of NP core in pre-formed membrane NVs	[112]
		Extrusion	• Avoids temperature-related damage • High reproducibility • Scalability • Uniformity of particle size	[113–115]
Blood protein-based	Albumin NPs	Desolvation/ crosslinking	• Avoids high temperature • Efficiency • Simplicity • Cost-effective	[116]
		Nab™	• Scalability • Controllable • Time-amenable • Size and stability uniformity • Safety	[117]
		HPH	• Scalability • Size and stability uniformity • Time-amenable • Versatility	[118]
	Ferritin NPs	Disassembly/ reassembly	• Time-amenable • Simplicity	[119,120]

which alternated cycles of freezing follow by thawing can disrupt cells' structure because of icy crystal formation and help releasing the inner contents, and membrane pellet is obtained after differential centrifugation [126–129]. This method is specially used for cancer cell membrane isolation because of simplicity, heat avoidance and maintenance of membrane protein stability. A membrane protein extraction kit protocol is also an interesting option for extracting cell membrane material [126–128,131], in which membrane protein content can be extracted by 1) either cell permeabilization, membrane protein release and solubilization followed by centrifugation for collecting membrane protein or 2) using buffers for extracting cell membrane proteins followed by purification step. The freeze-thaw method can be employed in combination with membrane extraction kits for enhancing the efficiency of cell lysis procedure and ensure complete disruption of the cell membranes [126–128]. For assembling cell membrane nanovesicles as an intermediate step, extrusion [110,129] or sonication [111,123,132] are often employed and cell membrane nanovesicles with size <200 nm and PDI <0.2 are produced. Cell membrane-coated structures are then prepared by extrusion or sonication of NP cores with cell membrane fragments or cell membrane nanovesicles [107,109,112,124,125,130]. Cell membrane nanovesicles are prepared by similar membrane extraction protocol (Fig. 3. G), followed by extrusion of cell membrane fragments, and can incorporate additional lipid components to improve stability, yield and functionality [113–115].

Protein-based bio-derived nanosystems such as albumin NPs and ferritin NPs are also subject of exploration regarding PC therapies. Regarding albumin NPs, a typical desolvation method allow production of stable drug-loaded NPs (Fig. 3. H). This method involves dissolving

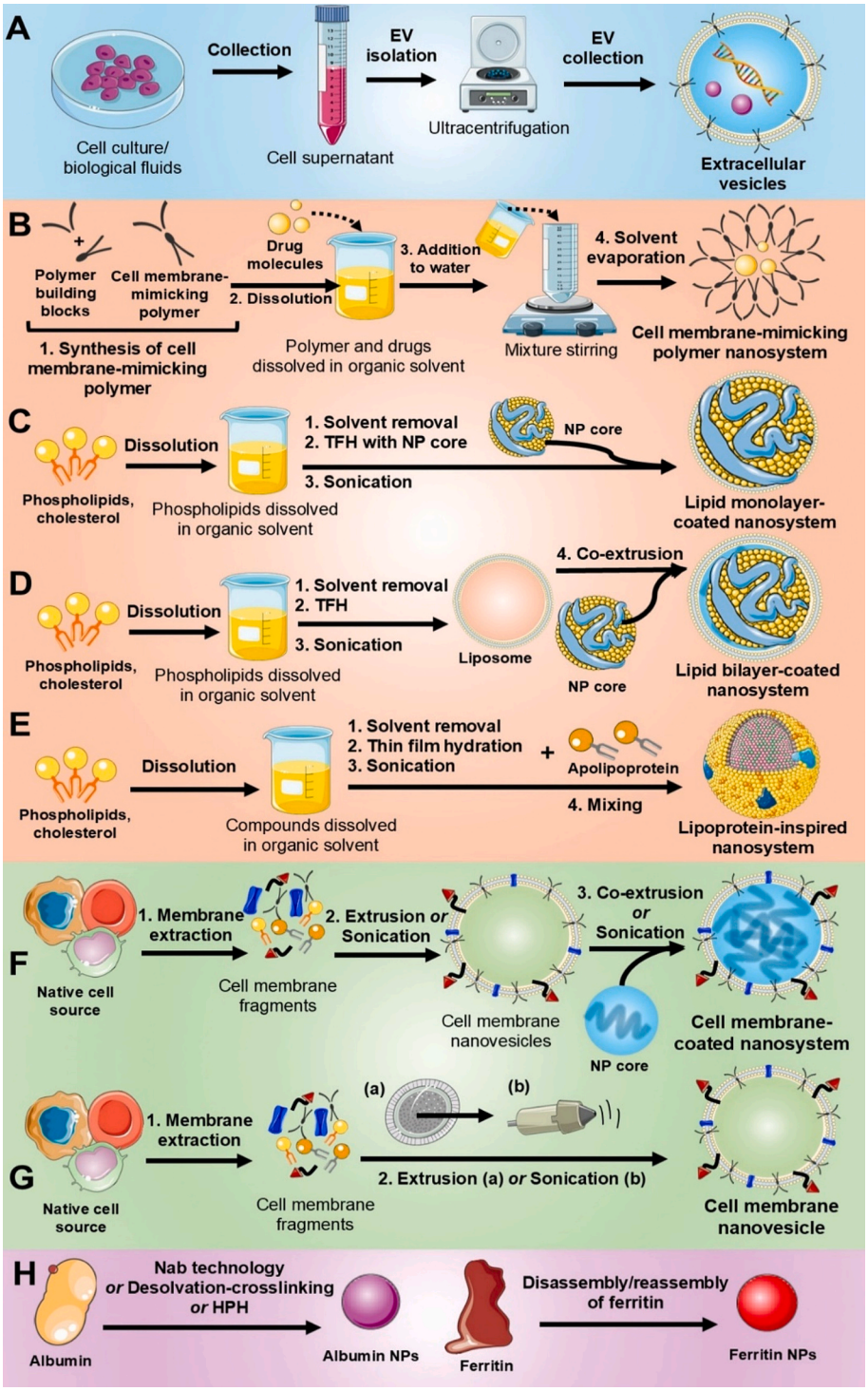

Fig. 3. Preparation of biomimetic nanosystems for pancreatic cancer therapies. (A) Extracellular vesicles (EVs) are often collected by ultracentrifugation; (B) Cell membrane-mimicking nanosystems can be prepared by traditional solvent evaporation method or dialysis; (C) Synthetic lipid monolayer-coated nanosystems are typically prepared by thin film hydration (TFH) method, although it is possible to obtain such systems by solvent evaporation method through self-assembly of the lipid layer around nanoparticle (NP) cores [121]; (D) Synthetic lipid bilayer-coated nanosystems are typically prepared by TFH method, and, similar to liposome preparation methods, an ethanol injection method derivative may be applied for coating NP cores by solvent evaporation [121]; (E) Lipoprotein-inspired nanosystems can be of distinct natures, and involve surface functionalization with lipoprotein moieties such as apolipoproteins. Their preparation conceals TFH method and subsequent addition of apolipoprotein and mixing; (F) Cell membrane-coated nanosystems have diverse preparation protocols, but the most frequent ones include extraction of membrane fragments through hypotonic lysis and differential ultracentrifugation, followed by co-extrusion of NP cores with membrane fragments or nanovesicles; (G) Cell membrane nanovesicles are similar in structure to EVs and are often prepared by extrusion of obtained membrane fragments; (H) Albumin nanosystems can be prepared by vast array of methods, including desolvation followed by crosslinking, and even the Nab™ technology that was incorporated in the clinically approved Abraxane®. Ferritin nanosystems are prepared by disassembly/reassembly of the ferritin's proteic structure.

Table 2
Overview of cell membrane extraction and cell membrane coating methods for preparing cell membrane-based biomimetic nanosystems for PC-targeted therapy.

Type	Cell type	Cell line	Membrane extraction	NVs preparation	Coating	Ref
Cell membrane-coated	Neutrophil	–	Hypotonic lysis buffer + differential ultracentrifugation	Extrusion	Co-extrusion NVs with NP core	[110]
	Macrophage	RAW 264.7		–	Co-extrusion of membrane fragments with NP core	[105]
					Co-extrusion of membrane fragments with NP core	[106]
	RBC	–			Sonication of membrane fragments with NP core	[108]
				Sonication	Sonication of NVs with NP core	[123]
	Neutrophil	–	Ultrasonication + differential ultracentrifugation + extraction kit		Co-extrusion NVs with NP core	[111]
	Cancer cell	BxPC3	Hypotonic lysis buffer + sonication + differential ultracentrifugation	–	Sonication of membrane fragments with NP core	[124]
		Panc02			Co-extrusion of membrane fragments with NP core	[107]
		KPC	Hypotonic lysis buffer + freeze-thaw + differential ultracentrifugation		Co-extrusion of membrane fragments with NP core	[125]
		BxPC3, SW1990, Panc-01	(Extraction kit) freeze thaw + differential ultracentrifugation		Sonication and co-extrusion of membrane fragments with NP core	[126–128]
		BxPC3	Freeze thaw + differential ultracentrifugation	Extrusion	Co-extrusion NVs with NP core	[129]
		BxPC3	Hypotonic lysis buffer + dounce homogenizer + differential ultracentrifugation	–	Co-extrusion of membrane fragments with NP core	[130]
		Panc02	(Extraction kit) lysis + differential ultracentrifugation		Co-extrusion of membrane fragments with NP core	[131]
	RBC	–	Centrifugation		Sonication of membrane fragments with NP core	[109]
	CAFs	–	Extrusion		Sonication of NVs with NP core	[112]
	Macrophage and Cancer cell	RAW 264.7 and Panc-1	Sonication + differential centrifugation	Sonication	Co-extrusion NVs with NP core	[132]
	RBC and cancer	BxPC3 and Panc2	Cancer cell membrane: (Extraction kit) lysis + differential centrifugation. RBC: hypotonic lysis buffer + centrifugation	Sonication + extrusion	Ultrasonication of NVs with NP core	[133]
Cell membrane nanovesicle	Cancer cell	Panc-1	Hypotonic lysis buffer + differential ultracentrifugation	Extrusion	–	[113]
	Dendritic cell EVs + liposome	–	Differential ultracentrifugation			[114]
	Platelet + liposome	–	Freeze-thaw + ultrasonication			[115]

albumin in aqueous solution, addition of desolvation agent for albumin dehydration, which then leads to conformational change and formation of albumin NPs, further stabilized by crosslinking procedure [116]. Nab™ technique is an efficient procedure for albumin NPs preparation and is supported by an emulsion-based rationale: high-speed homogenization of drug-containing organic phase and aqueous phase with albumin, high-pressure homogenization (HPH) of the mixture for NP preparation and organic solvent removal [117]. HPH can also be used isolatedly for preparing albumin NPs [118]. Ferritin NPs are commonly prepared through disassembly/reassembly process, in which ferritin structure is altered and NPs are prepared encapsulating desired drugs [119,120].

Of all nanosystems, EVs and cell membrane-based nanosystems comprise advantages such as superior targeting, biomimetic and tissue penetrating features. Cell membrane-coated nanosystems exhibit the best profile regarding combination of targeting abilities, drug loading versatility, coating tunability and multifunctionality. However, scale-up and complexity of the manufacturing process are two main challenges that need to be addressed for successful implementation of cell membrane coating technology. Table 3 provides a qualitative comparison between distinct biomimetic nanosystems explored for PC therapy, covering biological aspects (targeting potential and tissue penetration), stability, safety, technological features and scalability. Other reviews have covered in detail quantitative aspects of half-effective concentration (EC50) for targeting efficiency as well as *in vivo* blood circulation half-life, which provide useful information regarding targeting abilities and prolonged blood circulation of these systems, respectively [134–136].

2.2. Characterization of biomimetic nanosystems for PC therapy

The characterization of biomimetic nanosystems includes (1) physicochemical characterization, (2) biochemical characterization, and (3) additional characterization which evaluates drug release profile, stability, biocompatibility and targeting ability. The physical characterization recurs to techniques such as dynamic light scattering (DLS) for size measurement, population distribution - polydispersity index (PDI) -, and surface charge (zeta potential - ZP), and microscopy techniques like transmission electron microscopy (TEM), cryo-TEM or scanning electron microscopy (SEM) for adequate visualization of size, shape and structure of the nanosystems to assess its location as a thin sheet surrounding NP cores (appropriate thickness of 5–15 nm) [124], and drug loading and encapsulation efficiency [106,108]. In the case of cell membrane-coated nanosystems, additional experiments are often pursued for characterization of the cell membrane coating process, namely yield of the process, in which the extension of the coating process is analyzed, colocalization of the cell membrane coat through confocal laser scanning microscopy (CLSM) and stimulated emission depletion (STED) imaging [124,125,131], successful cell membrane hybridization, to attest formation of hybrid cell membranes, and orientation of the cell membrane surface repertoire ensuring right-side-in and the right-side-out. Biochemical characterization involves evaluation of surface functionalization moieties, which in the case of synthetic chemical conjugation processes may be accomplished by resonance magnetic imaging (RMN), Fourier transform infrared spectroscopy (FTIR), mass spectroscopy (MS) and in the case of cell membrane-based nanosystems employs BCA analysis for quantification of membrane protein content, SDS-PAGE

Table 3
Qualitative comparison of different properties of biomimetic nanosystems for pancreatic cancer therapy.

Property	EVs	Cell membrane-mimicking				Cell membrane-based		Blood protein-based
		CMMPs	LMCs	LBCs	LPIs	CMCNs	CMNs	
Targeting	+++	−	+	+	++	+++	+++	+
Blood circulation half-life	+++	+	+	+	++	+++	+++	++
Stability	+	++	++	++	+	+	+	++
Tissue penetration	++	+	+	+	++	++	++	++
Safety	++	+	++	++	++	++	++	+++
Inherent payload	−	++	++	++	++	++	++	++
Biomimetic features	+++	−	+	+	+	+++	+++	+
Drug loading versatility	+	++	++	+++	++	+++	++	+
Surface tunability	+	++	++	++	++	++	++	+
Size tunability	−	+	++	++	+	++	++	++
Manufacturing	−	++	+	+	+	−	−	+++
Yield	−	++	++	++	++	+	+	++
Scale-up	−	+	+	+	+	−	+	+++
Multifunctionality	+	−	+	+	+	+++	++	+

Abbreviations: EVs, extracellular vesicles; CCMPs, cell membrane-mimicking polymers; LMCs, lipid monolayer-coated nanosystems; LBCs, lipid bilayer-coated nanosystems; LPIs, lipoprotein-inspired nanosystems; CMCNs, cancer cell membrane-coated nanosystems; CMNs, cell membrane nanovesicles.
Label map: +++ (highly positive attribute), ++ (positive attribute), + (slightly positive attribute), − (negative attribute).

for analysis of protein expression in cell membranes extracted, cell membrane nanovesicles, and cell membrane-coated nanosystems [105], western blotting (WB) for evaluating expression profile of surface proteins expressed on cell membranes [105,106], immunofluorescence techniques to ascertain presence of surface markers and proteomic analysis [110].

3. Biomimetic nanosystems for PC therapy: Classification and applications

3.1. Extracellular vesicles

EVs are cell-derived nanostructures enclosing an aqueous core, with size typically ranging from 40 to160 nm and secreted by almost all cell types [137]. Exosomes are involved in cell-cell communication processes as they can transport a wide variety of cargo (*e.g.* lipids, proteins, nucleic acids) and deliver it to target cells, impacting both physiological and pathological processes [137]. For example, exosomes derived from GEM-resistant PC stem cells containing miR-210 were able to transfer its payload and mediate emergence of chemoresistance in GEM-sensitive PC cells, suggesting horizontal transfer of CT-resistant traits [138]. Moreover, EVs have been receiving particular attention as promising biomarkers for PC diagnosis and monitoring [139,140], and their implications in the complex crosstalk established among stroma cells (CAFs, immune cells) and cancer cells have been widely explored and thought to influence PC initiation, progression and metastasis [82,141–145].

Several studies have explored EVs as biocompatible, biomimetic drug delivery systems with intrinsic targeting features and low immunogenicity as strategy to modulate cancer progression [146–148]. Considering the reduced size, biomimetic nature, their multifunctional and biorelevant surface repertoire and tunable surface composition, EV-based drug delivery systems are versatile and attractive systems for PC therapeutics and can be used to shuttle therapeutic molecules to target sites with improved specificity and efficiency, as well as engaging in IT regimens driving immune activation and PC cells eradication, as summarized in Table 4.

Recently, GEM was loaded in autologous PC cell-derived exosomes aimed at increased cellular uptake when compared to heterologous exosomes [149]. GEM-loaded exosomes displayed increased PC targeting and biodistribution as opposed to GEM, as well as reduced toxicity [149]. Exosomal markers, namely tetraspanins (CD63, CD9, CD81), tumor susceptibility gene 101 (TSG101) and integrin-associated transmembrane protein (CD47) were detected successfully by western blotting. Another study aimed at exploring PC-homing properties of bone marrow mesenchymal stem cell (BM-MSC)-derived exosomes for PTX and GEM monophosphate targeted co-delivery to PC cells [91]. The exosomes reproduced surface repertoire of source cells as evidenced by the presence of tetraspanins (CD9, CD63), TSG101 and Flotillin-1. Researchers showed exosomes were able to penetrate desmoplastic stroma characterized by ECM hyperplasia and accumulate at tumor sites as shown in tumor spheroids and orthotopic model [91]. Other EV-assisted strategies to deliver PTX to PC were explored [155,157], as well as GEM [158], an adenosine prodrug [154] and anticancer and stroma reprogramming drug ormeloxifene [156].

The inherent homing properties were also explored to tackle low cancer immunogenicity and immunosuppressive microenvironment of PC *via* BM-MSC loaded with galectin-9 (Gal-9) siRNA and surface decorated with ICD inductor oxaliplatin (Fig. 4. A). Gal-9 is often expressed on the surface of PC cells and its interaction with macrophage receptor dectin 1 drives tumor associated macrophages repolarization from immunoactive M1-polarized tumor-associated macrophages (TAM) to immunosuppressive and pro-tumoral M2-polarized TAM. Gal-9 gene silencing *via* PC-targeted siRNA delivery was devised to inhibit Gal-9/ dectin 1 axis by downregulation of Gal-9 expression and induce TAM polarization towards M1 phenotype. Besides CT-mediated PC cells killing, combined oxaliplatin-mediated ICD and siRNA-mediated Gal-9/ dectin 1 axis remodeling boosted both cytotoxic T cell recruitment, T-cell mediated cytotoxic activity and macrophage reactivation. This strategy allowed immunosuppressive TME reversal by attacking in *two fronts* (Fig. 4. B-G) [159].

EVs may also improve nucleic acid delivery to PC cells through CD47-mediated immune evasion, selective targeting, and enhanced endocytosis. Exosomes derived from normal human foreskin fibroblast-like cells were loaded with short hairpin or small interfering RNA targeting $Kras^{G12D}$ oncogene and showed remarkable tumor growth suppression and improve survival in orthotopic and genetically engineered models [151]. KRAS silencing through extracellular vesicle systems was also reported in other studies recurring to mesenchymal stem cell exosome-loaded KRAS CRISPR-Cas9 plasmid DNA [152] and KRAS siRNA loaded in mouse embryonic fibroblasts or human BM-MSCs [153].

Another strategy was devised to silence oncogenic P21-activated kinase 4 (PAK4) gene through PAK4-specific siRNA (siPAK4) delivery to PC [93]. SiPAK4 was loaded in PC-derived exosomes *via* electroporation method (encapsulation efficiency *ca.* 16.5 %) and surface-expressed proteins included tetraspanins (CD9, CD63, CD81) involved in membrane fusion and cellular uptake, and CD47 which imparts immune escape properties to the exosomes. Intratumoral administration of siPAK4-loaded exosomes was shown to effectively silence PAK4 gene

Table 4
Extracellular vesicle-based nanosystems for PC-targeted therapies.

Origin	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
Autologous cancer cell-derived exosomes	GEM	–	70–150	–	i.v., 10 mg/kg GEM (3 times, 2-day interval)	PANC-1 mice xenografts	- High GEM loading - Tropism to parent cells - CD47–SIRPα binding-mediated immune escape-↑ tumor accumulation of GEM	[149]
MSC-derived exosomes	GEM + PTX	–	75	–	i.v., 10 mg/kg GEMP and equivalent dose of PTX (6 times each 3 days)	MiaPaCa-2 spheroids MiaPaCa-2 orthotopic mice	- ↑ tumor penetration - Tropism towards inflamed sites (chemotaxis) - Active and homotypic targeting *via* surface proteins - CD47-mediated prolonged blood circulation	[91]
BMSC-derived exosomes	miR-148a-3p	ITGA5 peptide	130–140	–	i.v.,EVs (100 μg/ mouse) 6 times, once every 3 days	PANC-1/CAF tumor-bearing mice	- surface functionalization with CAF-targeted peptide - ↑ CAF targeting and remodeling - miR-148a-3p delivery and integrin α5 (ITGA5) inhibition - ↑ tumor growth and downregulation of ITGA5	[92]
	miR-148a-3p + pirfenidone		163	–	several	PANC-1/CAF tumor-bearing mice (subcutaneous, orthotopic immunocompetent and orthotopic immunodeficient) + PDX model	- ↓ CAF activation and ↓ tumor growth - stroma remodeling, ↑ drug penetration and GEM activity - miRNA/pirfenidone combo enhanced therapeutic efficacy of GEM	[150]
Fibroblast-like mesenchymal cell exosomes	siRNA or shRNA $Kras^{G12D}$	–	–	–	i.p., 0.15–0.20 μg of exosomal protein/ injection.	PANC-1, BxPC-3, KTC $Kras^{G12D}$ orthotopic tumors KTC and KPC genetically engineered mice	- ↓ clearance from circulation - ↑ blood circulation half-life (mediated by CD47) - ↑ targeting to PC cells - ↑ uptake by PC cells - ↑ RNAi delivery and tumor growth suppression *vs* liposomes	[151]
PC cell-derived exosomes	PAK4 siRNA	–	97	−18	i.t., 0.03 mg/kg siPAK4 and 6.1×10^{11} exosome/dose (2 doses)	PANC-1 tumor- bearing mice	- ↑ gene silencing efficiency* - ↑ siRNA protection* - negligible *in vivo* toxicity* *when compared to Lipofectamine®	[93]
PC cell-derived exosomes	Chlorin e6	–	43	–	*In vitro*: 4 μg/mL based on membrane protein	MIA-PaCa-2 cells	-↑ Photoacoustic signal (5-fold) when compared with liposomes -↑ cellular uptake (4-fold) when compared with liposomes - ↑ cytotoxic effect after laser irradiation when compared with free Ce6	[94]
Immunogenically dying PC cell-derived exosomes	CCL22 siRNA	MART-1 peptide	73	–	10^8 exosomes/mouse, once a week for 3 weeks	PANC-2 tumor- bearing mice	- ↓ T regulatory cells expansion (inhibition of CCR4/ CCL22 axis) - immunostimulatory properties displayed by MART-1 peptide - exosome-mediated antigen presentation - ↑ immune sytem activation - synergistic anticancer response when combined with GEM and Abraxane®	[142]

(*continued on next page*)

Table 4 (*continued*)

Origin	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
MSC-derived exosomes	$Kras^{G12D}$ CRISPR/Cas9–encoded pDNA	–	~150	–	i.v. and i.t. injection 10^9 exosomes/mouse, 10 μg plasmid DNA, during 2 weeks, every other day	KPC689 tumor- bearing mice	- efficient delivery of CRISPR/Cas9–pDNA - $Kras^{G12D}$ inhibition - organotropic features - ↓ tumor proliferation	[152]
MEF- or hBMSC-derived exosomes	$KRAS^{G12D}$ or TP53 siRNA	$CD64^{CK}$ + αROR1 antibody	62–118	–	i.p. injection 1×10^{11} exosomes/mouse, 3 times/week, GEM 20 mg/kg 1/week	PANC-1 tumor- bearing mice PDXs	- ↑ PC targeting by CK peptide and CD64 protein - ↑ PC targeting by anti-αROR1 - ↑ tumor growth inhibition when combined with GEM	[153]
PC- and macrophage-derived exosomes	Adenosine-peptide prodrug	–	159/125	−12/−27	–	AsPC-1 cell line	- ↑ adenosine stability - cathepsin B-activatable prodrug - ↑ macrophage-derived exosome production *vs* PC-derived exosomes - ↑ loading, cell uptake and anticancer activity for PC-derived exosomes	[154]
HEK 293 cell-derived exosomes	PTX	RGD + $CD47^{p110–130}$	–	–	i.p. GEM administration (100 mg/kg), 2 times/week for 4 weeks, 10 mg/kg PTX (30 μg exosomes) 5 times, 5 consecutive days	PDCL5 tumor-bearing mice	- CD9-mediated anchoring of double targeting molecules RGD and CD47p110–130 - ↓ macrophage uptake through $CD47^{p110–130}$ – SIRPα axis - ↑ PC targeting by RGD (overexpressed αvβ3 integrins on PC cell membrane)- ↑ anticancer activity and tumor suppression for PTX-loaded exosomes in combination with GEM	[155]
NAF-derived exosomes; CAF-derived exosomes	ORM	–	272/216	−20/−17	i.p. administration, 200 μg, 5 times, twice a week	HPAF-II/stroma cells tumor-bearing mice	- ↑ drug loading for NAF exosomes - PC-targeted features of NAF exosomes - ↓ stroma desmoplasia and EMT (NAF exosomes) - ↓ tumor growth (NAF exosomes)	[156]

Abreviations: NPs, nanoparticles; ZP, zeta potential; GEM, gemcitabine; i.v., intravenous; SIRPα, Signal regulatory protein α; MSC, mesenchymal stem cell; PTX, paclitaxel; GEMP, gemcitabine monophosphate; siRNA, small interfering RNA; i.p., intraperitoneal; PC, pancreatic cancer; i.t., intratumoral; CCL22, chemokine ligand 22; CCR4, C—C chemokine receptor type 4; pDNA, plasmid DNA; CRISPR/Cas9, clustered regularly interspaced palindromic repeats/CRISPR-associated protein 9; MEF, mouse embryonic fibroblasts; hBMSC, human bone marrow stromal cells; αROR1, receptor tyrosine kinase-like orphan receptor 1; RGD, arginylglycylaspartic acid; NAFs, Tumor adjacent fibroblasts; CAF, cancer-associated fibroblasts; ORM, ormeloxifene; EMT, epithelial mesenchymal transition.

and delay PC progression. Other studies have explored double targeted EVs for nucleic acid delivery, namely C—C motif chemokine 22 (CCL22) siRNA delivery [142] and surface functionalization with PC-targeted CKAAKNK (CK) peptide anchored to Fc-γ receptor 1 CD64 and anti-receptor tyrosine kinase-like orphan receptor 1 (αROR1) also targeting PC cells [153]. A recent study showed BMSCs-derived EVs modified with integrin α5 (ITGA5) could efficiently deliver ITGA5-targeting miRNA to CAFs and exert down-regulation of ITGA5, Proliferating Cell Nuclear Antigen (PCNA), Actin α2, Smooth Muscle (ACTA2), and Fibroblast-Specific Protein (FSP) [92]. Combination of ITGA5-targeted miRNA with pirfenidone showed encouraging results in several mice models of PC by enhanced stroma remodeling, increased GEM therapeutic activity and suggested maximized anticancer response when combining GEM with the pirfenidone/miRNA co-loaded EVs [150].

In another study, PC cell line-derived exosomes were obtained, and their internal content was removed. The re-assembled exosomes loaded with hydrophobic photosensitizer Chlorin e6 (Ce6) were developed to achieve photoacoustic imaging-guided combined cancer photodynamic therapy and IT of PC (Fig. 5. A) [94]. The exosomes were able to recapitulate surface membrane proteins (CD9, CD63 and CD81) and retained source-cell targeting properties. PA helped monitoring Ce6 delivery and accumulation at tumor tissues, and intrinsic immunogenic surface repertoire of tumor-derived exosome membranes containing tumor-specific antigens stimulated immune responses (Fig. 5 B-E).

Immune activation was reported in immune cells, namely increased cytokine secretion and macrophage polarization to M1 in murine macrophage cells, which can be used as immunotherapeutic component [94]. While *in vivo* studies were performed in B16F10 engrafted mice models, this strategy can potentially be applied to other solid tumors and evidencing special relevance for preventing tumor relapse (Fig. 5. F—H). This strategy avoids off-target damage to distant tissues and other cells such as immune cells due to preferential accumulation of the photosensitizer in cancer tissues and therefore to the localized tissue damage triggered by laser irradiation. Recent study employing ICG and STING agonist SR-717 co-encapsulated in Panc-2 cell-derived exosomes showed promising anticancer results by enhancing photo-immunotherapy with improved safety [160]. Near-infrared light irradiation lead to exosome rupture and release of STING agonist and promoting PC-specific STING pathway activation with consequent boosting immunogenicity and antigenicity of the nanosystem towards

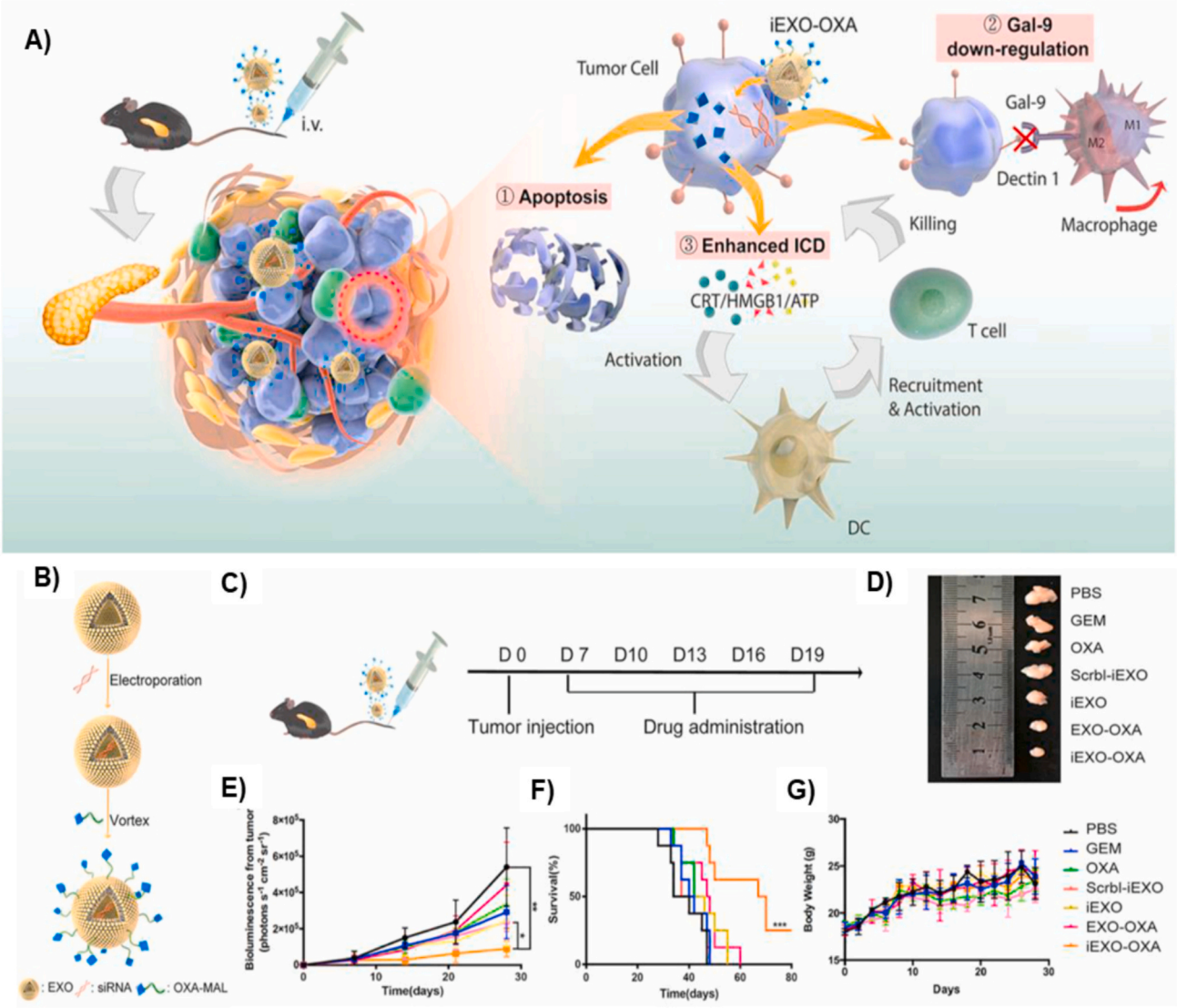

Fig. 4. (A) Schematic illustration of the pancreatic cancer-targeted exosomes enabling enhanced immunotherapy and reprogramming TME. The mechanistic approach involved 1) OXA-mediated tumor cell apoptosis, 2) Galectin-9 down-regulation followed by macrophage polarization and 3) OXA-mediated ICD activity. (B) Preparation of iEXO-OXA. (C-G) *In vivo* antitumor activity of iEXO-OXA, namely (C) *in vivo* administration schedule; (D) Tumor size evaluation; (E) Bioluminescence evaluation; (F) Survival rate and (G) Body weight of the mice during the 4-week treatment course. Adapted with permission from [159]. Copyright Elsevier (2020). *Abbreviations:* TME, tumor microenvironment; ICD, immunogenic cell death; CRT, calreticulin; DC, dendritic cell; OXA, oxaliplatin.

PC eradication.

Finally, bacteria-derived vesicles (OMVs) can also be explored as highly tunable biomimetic nanosystems for drug delivery towards PC [161,162]. OMVs comprise lipid bilayer nanostructures that are actively released by gram-negative bacteria bearing similar structure to cell-secreted EVs and incorporate interesting biomimetic, immunogenic and tailored features of relevance towards developing innovative drug delivery and vaccination systems [161,162]. A recent example is the isolation of *Escherichia coli* Nissle 1917 and further modification with nerve-binding peptide, which can target PC-associated nerves and deliver larotrectinib, a tropomyosin receptor kinase inhibitor, and improve GEM therapeutic efficacy *in vivo* [163].

3.2. Synthetic cell membrane-mimicking nanosystems

Cell membrane-mimicking nanosystems consist of synthetic systems that partially resemble the structure and function of cell membranes, and have been prepared either by polymer modification for mimicking phospholipids, coating of NP cores with either lipid monolayers or lipid bilayers, and by mimicking lipoproteins (Table 5).

3.2.1. Phospholipid-mimicking nanosystems

Phospholipids represent the main constituents of cell membranes and have an amphiphilic structure composed of hydrophobic fatty acid chains and a hydrophilic glycerol head. In an attempt to build a polymer-based phospholipid-mimicking structure with self-assembly properties, researchers increased the length of alkyl chain to zwitterionic monomer 2-methacryloyloxyethyl phosphocholine to improve its structural similarities to phospholipids, followed by reversal addition−fragmentation chain transfer (RAFT) polymerization to yield amphiphilic poly(12-(methacryloyloxy)-dodecyl phosphorylcholine) (PMDPC) homopolymer. PMDPC was able to form micellar structures bearing phospholipid-mimicking layer, a hydrophobic core and zwitterionic phosphorylcholine shell for prolonging blood circulation of a near-infrared dye (Table 5) [95]. The theranostic micelles composed of PMDPC showed enhanced IR-780 biodistribution at tumor sites as well as improved *in vivo* tumor imaging and photothermal effect on PC-bearing xenograft models [95].

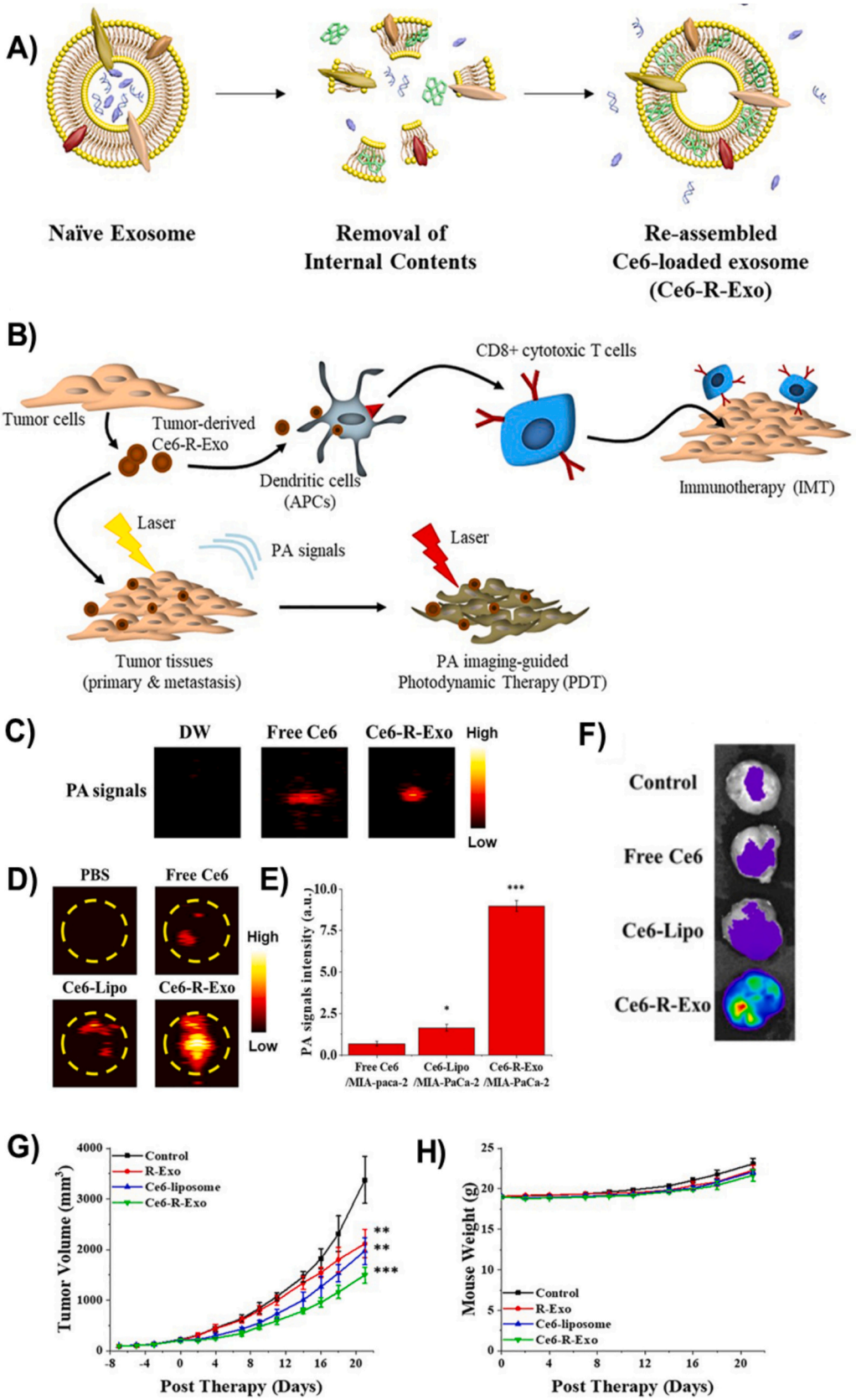

Fig. 5. Schematic illustration of Ce6-R-Exo system, namely (A) fabrication of Ce6-loaded exosomes, (B) combination of PDT and IT associated with PA imaging guidance, (C) background PA signals for free Ce6 and Ce6-R-Exo, (D) *in vitro* PA images of free Ce6, Ce6 loaded liposome (Ce6-Lipo), Ce6-R-Exo treated MiaPaCa-2 cells; (E) quantification of of PA signals of tested formulations (D). (F) *In vivo* distribution of intravenously injected Ce6-R-Exo in B16F10 mice tumor model. (G) Tumor volume and (H) body weight variation after PDT alone (Ce6-liposome), IT alone (R-Exo) and the combination of PDT and IT (Ce6-R-Exo). Adapted with permission from [94]. Copyright Elsevier (2020). *Abbreviations:* Ce6, chlorin e6; PA, photoacoustic signal; PDT, photodynamic therapy, IT, immunotherapy.

Table 5
Examples of cell membrane-mimicking nanosystems for PC-targeted therapies.

Nanosystem	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
Phospholipid-mimicking nanosystems								
PMDPC homopolymeric micelles	IR 780	–	160	–	i.v. PMDPC-IR780 micelles, 0.5 mg/kg IR-780 equivalent	BxPC-3 subcutaneous	- ↑ tumor tissue accumulation of IR 780 - Image-guided photothermal therapy - ↑ photothermal effect	[95]
Synthetic lipid monolayer-coated nanosystems								
NaLuF4:Yb, Tm /NaLuF4/NaDyF4 UCNPs with PC coating	–	–	68	−38	i.v. or i.p., 0.2 mL, 3.0 mg/mL	MIA-PaCa-2 orthotopic	- ↑ blood and lymphatic circulation owing to PC coating - ↑ tumor homing and cell uptake (i.p.) - ↑ tumor biodistribution (i.p.) - Deep tumor tissue penetration (120 μm) (i.p., 980 nm laser power density 0.5 W/cm^2)	[96]
GEM-phytanyl, DMPC, Cholesterol lipid NPs	GEM	–	136	–	i.v., twice a week /4 week (equivalent of 4.19 mg of free GEM/kg)	NOD/SCID mice-bearing subcutaneous tumor	- Enzyme-responsive GEM release - GEM controlled release - ↓ tumor size when compared to free GEM	[97]
Synthetic lipid bilayer-coated nanosystems								
Lipid bilayer-coated GO@AuNS	KRAS pDNA	FA	51.3	26	i.v., GO@AuNS, 0.6 mg/mL, + pKras, 1 μg	Capan-1 cells; Subcutaneous Capan-1 tumor-bearing mice	- ↑ tumor tissue accumulation - ↑ photoacoustic and photothermal heating of tumors - Tumor growth inhibition *ca.* 98.5 % (800 nm, 1.2 W/cm^2/ 10 min)	[98]
Lipid bilayer-coated silicasome	GEM + PTX (10:1)	–	75	–	i.v, particle dose of 250 mg/kg (GEM, 100 mg/kg; PTX, 10 mg/kg), 6 times in 38 days	PANC-1 orthotopic mode	- ↓ PC stromal volume* - ↑ tumor growth inhibition* - ↑ concentration of GEM active metabolite* - ↓ concentration GEM inactive metabolite* *when compared to GEM+Abraxane®	[99]
Lipid bilayer-coated silicasome	IRT	–	80	−22	i.v., formulation containing 40 mg/kg, 4 days, up to 8 times	KPC-derived orthotopic model	- ↑ tumor tissue accumulation of drug-loaded silicasomes* - ↑ anticancer performance* - ↓ toxicity* *when compared to free drug and liposomal counterparts	[100]
Lipid bilayer-coated silicasome	IRT	–	130	−10	i.v., 40 mg/kg IRT; 80 mg/kg MSNs; 8 μmol/kg free iRGD, 3 days, 4 times	KPC-derived orthotopic model	- ↑ tumor biodistribution when compared to iRGD-coupled silicasomes - ↑ anticancer performance following free iRGD is co-administration	[101]
PEGylated lipid bilayer-coated silicasome	IRT	–	–	–	i.v., equivalent 40 mg/ kg IRT + i.p. administration of 100 μg anti-PD-1, every 3 days, 6 times	KPC-derived orthotopic model	- ↑ anticancer performance when anti-PD-1 administered - ↑ ICD response for IRT-loaded silicasome *vs.* free IRT - ↑ mice survival when compared to Onivyde® + anti-PD-1combination	[102]
PEGylated lipid bilayer-coated silicasome	IND + OXA	–	100	−5	i,v, equivalent 5 mg/kg OXA and 50 mg/kg IND, 4 times each 4 days	KPC-derived orthotopic model	- ↑ interference IDO pathway (↑P-S6K and ↓IL-6 mRNA levels) - ↑antimetastatic performance - ↑ cytotoxic T cells/ regulatory T cells ratio-Innate and adaptive immune responses	[103]
Lipid bilayer-coated silicasome	Nintedanib	–	126	−8	i,v, equivalent 10 mg/kg nintedanib +10 mg/kg anti-PD-1, 2 times/week for 2 weeks	KPC-derived orthotopic model	- triple targeting of TME-expressed receptors - stroma remodeling (ECM	[164]

(*continued on next page*)

Table 5 (*continued*)

Nanosystem	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
							and vasculature) - ↑ PD-L1 expression in PC cells - combination with anti-PD-1 antibody - ↑ immune systema activation when combined with anti-PD-L1	
Liposome-coated polyplex	GEM-lipid prodrug + IL12 pDNA + JQ1	AEAA	161	−10	i.v., equivalent 10 mg/kg JQ1, 10 μg/mouse pIL12, 7.5 mg/kg GEM prodrug, 5 mg/kg C18 ceramide (4 times, 3 days interval)	PANC-2/NIH3T3 tumor-bearing mice (subcutaneous and orthotopic)	- stroma targeted system (AEAA) - stroma remodeling - ↑ immune cell infiltration, helped by IL-12 - C18 ceramide enables GEM-loaded exosome secretion - enzyme-responsive GEM release - ↑ immunoactive TME - ↑ chemo-IT when compared to controls	[165]
PEGylated lipid bilayer-coated silicasome	IRT + TLR7/8 agonist 3 M-052-C18	–	127	−13	i.v., equivalent 2 mg/kg 3 M-052, 40 mg/kg IRT, every 3 days, 4 times	Subcutaneous/ orthotopic KPC tumor-bearing mice	- TLR7/8 agonist encapsulated in the lipid bilayer by coupling to C18 lipid tail - ↑ ICD effect of IRT in combination with 3 M-052-C18 - ↑ DC activation and T cell infiltration - ↓ Regulatory T cells	[166]
PEGylated lipid bilayer-coated silicasome	DACHPt	–	138	~ −33	i.v., equivalent 2 mg/kg DACHPt, every 3 days, 3 times + i.p. administration of 100 μg anti-PD-1, 2 days after DACHPt administration	Orthotopic KPC tumor-bearing mice	- Activated Pt drug loading and delivery - ↑ DACHPt pharmacokinetic profile and therapeutic effect - ↓ bone marrow toxicity - Strong ICD induction - ↑ survival for group treated in combination with anti-PD-1	[167]
Lipid bilayer-coated polyplex	CAR pDNA + CD47 inhibitor (RRx-001)	Arginine	164	−11	i.v. pDNA dose of 1.2 mg/kg, RRx-001 dose of 10 mg/kg, 4 day interval between injection	Orthotopic hMUC1^{+} tumor-bearing mice	- cationic mannosylated chitosan oligosaccharide-arginine for pDNA complexation and nucleus targeting - CD47-derived D-mouse "self" peptide exposed at the bilayer - CAR gene delivery to intratumoral macrophages - *in situ* generated CAR macrophages - ↑ tumor inhibition and long-term immune memory	[168]
Lipoprotein-mimicking systems								
Lipoprotein mimicking vesicle (DMPC/DSPE-PEG-HC8/APOA1 peptide)	FO (OXA + furoxan)	HC8 + ApoA1	22	–	i,v, equivalent 5 mg/kg OXA 6 times, intercalated with 6 times i.t. anti-PD-L1 0.1 mg/kg	PANC-2 tumor-bearing mice	- Redox-responsive system - OXA as double-acting drug (cytotoxic activity and TAM reprogramming) - HC8-mediated TME targeting (stroma, endothelial cells and TAM) - ApoA1 targeting of TAMs - NO release and normalization of vasculature - ↑ anticancer activity when combined with anti-PD-L1	[122]
GEM-phytanyl, DMPC/ Cholesterol/APOA2	GEM	ApoA2	130	−33	i.v., equivalent 4.45 mg/kg GEM, 200 μL, twice week/4 weeks)	CFPAC-1, PDX-8, PDX-13 and Panc-1 NOD/SCID mice xenografts	- ↑ targeted delivery of GEM to PC - ↑ anticancer performance, particularly in less stroma-rich models (PANC-1, PDX-8)	[104]

Abreviations: NPs, nanoparticles; ZP, zeta potential; PMDPC, poly(12-(methacryloyloxy)dodecyl phosphorylcholin); GEM, gemcitabine; i.v., intravenous; i.p., intraperitoneal; PC, pancreatic cancer; i.t., intratumoral; UCNP, upconversion NPs; DMPC, 1,2-dimyristoyl-sn-glycero-3-phosphocholine; GO@AuNS, graphene oxide/gold

nanosheets; PTX, paclitaxel; IRT, irinotecan; FA, folic acid; MSN, mesoporous silica NPs; PD-L1, programmed cell death ligand 1; PD-1, programmed cell death protein 1; OXA, oxaliplatin; IND, indoximod; ICD, immunogenic cell death; IDO, indoleamine 2,3-dioxygenase; TME, tumor microenvironment; ECM, extracellular matrix; IL12 pDNA, interleukin 12 plasmid DNA; JQ1, BET inhibitor; ApoA1, apolipoprotein A1; ApoA2, apolipoprotein A2.

3.2.2. Synthetic lipid monolayer-coated nanosystems

NPs composed of NaLuF4:Yb,Tm and further modified with NaLuF4/NaDyF4 were explored as multimodal contrast agent-enabled nanosystem for maximized PC imaging after intraperitoneal injection [96]. Dysprosium [169], a rare earth element bearing T2 contrast imaging properties, was doped into NPs endowing them with magnetic resonance imaging (MRI) abilities, and a NaLuF4-composed shell introduced excellent upconversion luminescence (UCL) properties to the nanosystem. To improve biocompatibility, bioavailability and biomimetic features of UCNPs, a phosphatidylcholine coating was employed to cover UCNPs (UCNP@PC). *In vivo* studies in orthotopic PC-bearing mice showed marked targeted accumulation at tumor sites detectable after 7 days of intraperitoneal injection suggesting long-term retention of UCNP@PC in PC tissues, as opposed to absence of signal after 7 days and enhanced liver accumulation of UCNP@PC in mice subjected to intravenous injection. PC coating could have played a role in enhancement of tumor penetration of the UCNP@PC as it could potentially have favored tissue accumulation and diffusion among cells because of the similarity to lipidic constituents of cell membranes and by conferring enhanced fluidity. The UCNP@PC could potentially embody an interesting biomimetic strategy for contrast-enhanced MRI of PC. Of interest, the UCNP@PC showed safety as it could be cleared out rapidly *via* hepatobiliary pathway avoiding unwanted subsequent accumulation [96]. In addition, both lipid monolayer of phosphatidylcholine and high density lipoprotein layer have also been reported to coat citrate gold NPs and silica gold nanoshells, showing enhanced tumor penetration than PEGylated ones and suitability for PC imaging [170,171].

Oncogenic mutations in KRAS gene are one of the key drivers in PC progression and occur in approximately 90 % of cases [172]. A recent strategy was devised to silence mutated KRAS gene through delivery of KRAS-targeted siRNA (siKRAS) using lipoprotein-mimicking biomimetic NPs [173]. Briefly, calcium phosphate NPs encapsulating siKRAS *via* electrostatic interactions were coated with lipid monolayer containing apolipoprotein E3 (ApoE3), a glycoprotein with relevant functions in lipid transport and metabolism and used to improve tumor biodistribution of the NPs (Fig. 6. A). siKRAS-loaded NPs was used in combination with CGKRK-coupled PEG-PLA NPs encapsulating antifibrotic drug fraxinellone targeting overexpressed heparan sulfate proteoglycan glycoproteins expressed in PC TME and aimed at inactivating transforming growth factor beta (TGF-β) pathway and promoting stroma normalization. Stroma modulation achieved by fraxinellone-loaded nanosystem enhanced perfusion of the siKRAS-loaded nanosystem and resulted in improved KRAS silencing performance of the nanosystem and improved overall survival (Fig. 6. B-E) [173].

3.2.3. Synthetic lipid bilayer-coated nanosystems

CT delivery *via* self-assembled drug conjugates has also been explored for achieving controlled and stimuli-sensitive delivery of CT at tumor sites. For example, gemcitabine [28] was conjugated to lipids (*e.g.* phytanyl) forming a prodrug conjugate system [97]. Then, GEM-phytanyl prodrug amphiphiles were combined with 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and cholesterol to form liposome-like lipid structures with self-assembly properties which, upon cleavage of carbamate bond between GEM to lipidic chains by carboxylesterase 2, were able to release GEM in a controlled release fashion [97]. The amphiphilic prodrug nanosystem with self-assembling properties was developed on an attempt to minimize drug leakage, burst release and improve encapsulation efficiency, and showed core-shell structure suggesting incorporation of the prodrug into lipid bilayer. The CES2-responsive nanosystem evidenced excellent bioconversion of GEM-phytanyl to active GEM, was able to remain in circulation for over 48 h, and exerted higher antitumor performance when compared to free GEM.

While graphene oxide has interesting photothermal properties, combination with other NIR-absorbing structures such as gold-based NPs may improve overall photothermal (808 nm) performance and imaging capabilities. In this regard, Jia et al. developed mutant KRAS gene plasmid-loaded reduced graphene oxide-gold nanostar hybrid complexes (GO@AuNS) for concerted photothermal therapy, gene therapy and photothermal-photoacoustic dual imaging of PC (Fig. 7. A) [98]. To improve stability, biocompatibility and targeting of GO@AuNS complexes, a folic acid-functionalized lipid bilayer was employed as coating of the complexes, significantly decreasing their size and increasing zeta potential to positive values (Table 5). Lipid bilayer-coated GO@AuNS showed enhanced photoacoustic imaging and heat-converting properties on PC-bearing mice model (Fig. 7. B-E). The mice treated with pKRAS-loaded GO@AuNS complexes under laser radiation showed the best tumor reduction (Fig. 7. F-G) and suppressed liver metastasis, showing that the combination of gene with photothermal therapy may potentially advance future theranostics of PC.

Lipid bilayer coating was also explored with other inorganic nanomaterials, namely MSNs, towards PC-targeted nanotherapies (Table 5). For example, lipid bilayer-coated mesoporous silica NPs (MSNs), also known as silicasomes, were prepared and co-loaded with synergistic combination of CT drugs GEM and PTX, recurring to a coated lipid film method [99]. Besides providing a hydrophilic stealth and more biocompatible interface to the nanosystem, lipid bilayer coating enabled to maximize coating procedure, higher GEM loading without leakage by acting as a lipidic seal and provided hydrophobic compartment for hydrophobic PTX encapsulation. The co-loaded lipid bilayer-coated MSNs showed enhanced synergistic anticancer activity, tumor volume reduction and depletion of stroma volume in PC-bearing mice models when compared to conventional combination of free GEM and Abraxane®. Also interestingly, lipid bilayer-coated MSNs encapsulating IRT minimized systemic drug leakage when compared to IRT-loaded liposomes [100], thus showing superior stability, improved IRT release profile and reduced toxicity. In another study, co-administration of peptide CRGDKGPDC (iRGD) enhanced the uptake of IRT-loaded silicasomes by PC cells [101] and exhibited better tumor penetration and biodistribution when compared to iRGD-functionalized silicasome counterparts (Fig. 8. A-B). Additionally, this strategy enables to circumvent complex chemical conjugation processes for attaching iRGD to the surface of silicasomes and bypasses the limited expression density of targeting receptors expressed at tumor site and correspondent ligands coupled to the surface of the silicasome. The mechanism may be related to free iRGD binding to $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins expressed more abundantly in tumor-associated vasculature followed by proteolytic cleavage of iRGD and exposition of its C terminal motif, which interacts with neuropilin-1 receptor promoting substantial internalization of silicasomes *via* a transcytosis process. Co-administration of free iRGD with IRT-loaded silicasomes outperformed anticancer activity achieved by sole IRT-loaded silicasome injection (Fig. 8. C) [101].

Combination of IRT-loaded silicasomes with ICB inhibitors was also explored towards chemoimmunotherapy of PC. The combination of IRT-loaded PEGylated silicasomes with free anti-PD-1 antibodies was able to improve the anticancer performance through a chemo-immunotherapeutic effect by immune reactivation of PC TME further potentiated by ICB inhibitors delivery [102]. The mice treated with sole IRT-loaded silicasomes or onivyde® - a commercial formulation of liposomal IRT – showed similar survival outcome, whereas the ones treated with silicasome-anti-PD-1 combination showed remarkably extended mice survival. Combination of CT drugs capable of triggering immunogenic cell death responses, such as IRT and OXA, with metabolic pathways inhibitors is also an interesting strategy to modulate PC TME and improve T cell recruitment and activation for more effective

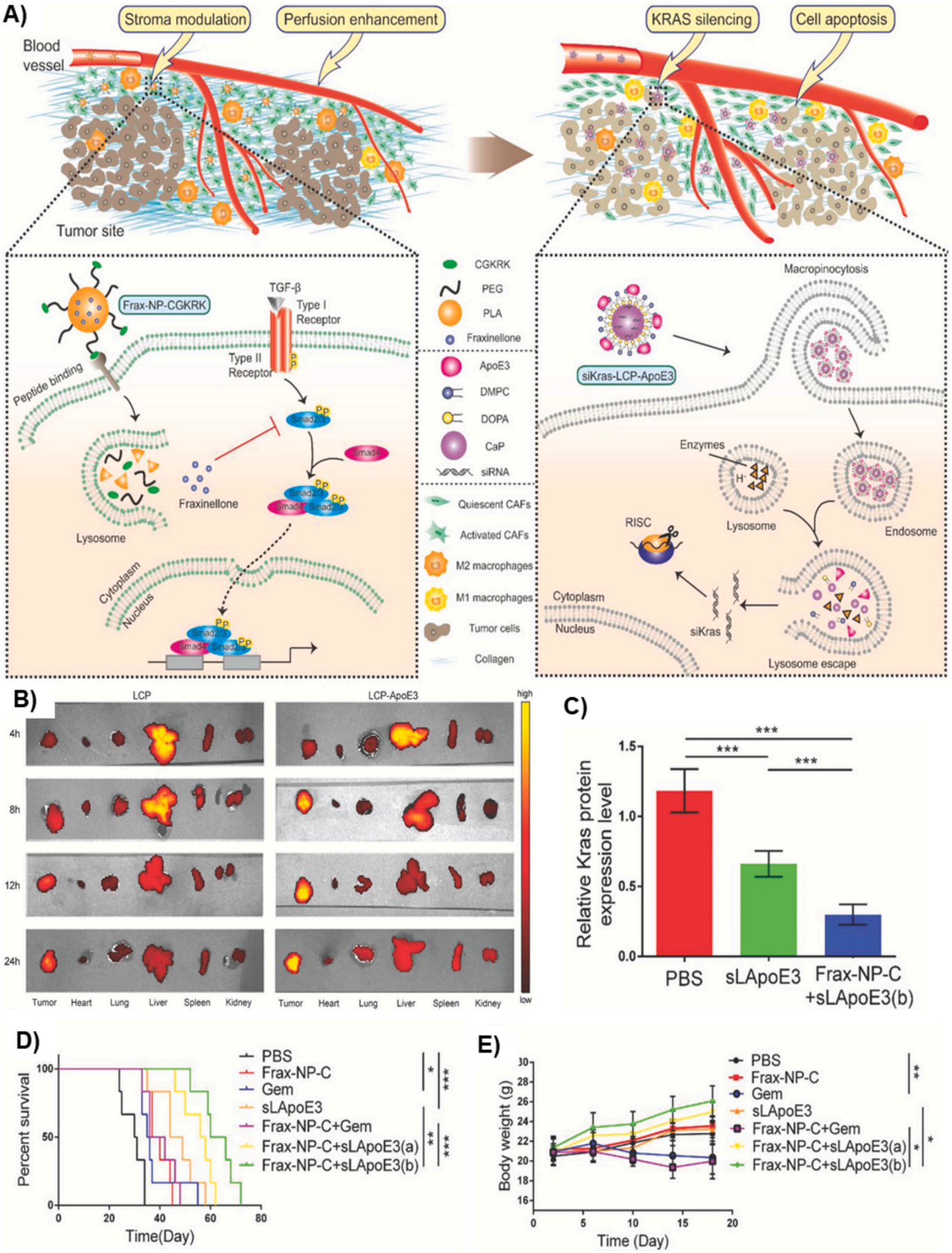

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Fig. 6. (A) Schematic illustration of the mechanism underlying administration of fraxinellone-loaded CGKRK-modified PEG-PLA NPs (Frax-NP-CGKRK) and KRAS siRNA (siKRAS)-loaded biomimetic NPs (siKRAS-LCP-ApoE3). As first step, Frax-NP-CGKRK is intended to modulate the PC stroma by CAFs inactivation and by depleting M2 macrophages *via* pSmad2/3 signal inhibition in the TGF-β/Smad pathway. Then, tumor blood vessels are normalized, and blood perfusion is enhanced, which then facilitated the penetration and diffusion of siKRAS-LCP-ApoE3 system, which was internalized by PC cells through macropinocytosis. (B) Fluorescence intensity of DiR-labeled LCP and LCP-ApoE3 (20 mg/kgDMPC) at 4, 8, 12, and 24 h post-injection in tumors and major organs (heart, lung, liver, spleen, and kidney), showing Frax-NP-CGKRK facilitated the tissue permeation of siRAS-LCP-ApoE3 system. (C) KRAS protein expression levels in tumor tissues of siKras-LCP-ApoE3 and Frax-NP-C + sLApoE3(b) groups. (D-E) Therapeutic efficacy of Frax-NP-CGKRK, Gem, siKras-LCP-ApoE3, Frax-NP-C + Gem, Frax-NP-C + sLApoE3(a), and Frax-NP-C+ sLApoE3(b) on orthotropic tumor models. (D) Tumor survival rates, (E) body weight monitoring. Reproduced with permission from [173]. Copyright John Wiley & Sons (2019). *Abbreviations:* PEG-PLA, poly(ethylene glycol)-poly(lactic acid); siKras, anti-KRAS siRNA, NPs, nanoparticles; LCP, lipid calcium phosphate; ApoE3, apolipoprotein E3; CAFs, cancer-associated fibroblasts; TGF-β, Transforming growth factor- β; DiR, 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide; DMPC, Dimyristoylphosphatidylcholine.

therapeutic immune responses in PC. A recent strategy consisted of oxaliplatin-loaded PEGylated silicasomes in which the lipid bilayer was result of self-assembled nanovesicles made of IDO pathway inhibitor indoximod-phospholipid amphiphiles bearing labile ester bond, which self-assembled into lipid prodrug nanovesicles used to coat MSNs (Fig. 8. D) [103]. The nanosystem showed both enhanced tumor biodistribution and intratumoral concentration of IND and OXA, as well as interesting immune suppression reversal properties by a synergistic 2-in-1 approach (Fig. 8. E-F).

Silicasome-based systems were further explored for delivery of triple protein tyrosine kinase inhibitor nintedanib to improve IT response (*e.g.* anti-PD-1) in PC model [164]. Nintedanib was chosen due to its interesting triple action in targeting several receptors overexpressed in PC TME, namely vascular endothelial growth factor, platelet-derived growth factor and fibroblast growth factor ones, showing a multifunctional interplay among TME vasculature, stroma and immune cells. The improved anticancer effects were attributed to concerted stroma remodeling by structural normalization of blood vessels (evidenced by diminished CD31 staining density suggestive of reduced vasculature density) for augmented permeability, enhanced recruitment of cytotoxic T cells and reduced infiltration of immunosuppressive regulatory cells. The system was able to leverage response to ICB inhibitor anti-PD-1 and elicit strong immune responses in an orthotopic PC model. The combination of IRT with toll-like receptor TLR7/8 agonist was able to leverage IRT-mediated ICD [166]. IRT was loaded in the pores of MSNs and protected by the lipid bilayer, which served as a biocompatible shell for inserting C-modified TLR7/8 agonist, which limits its off-target inflammatory effects. The nanosystem elicited a synergistic immune response by combined delivery of both cargoes, as ICD-mediated by IRT is able to release tumor cell antigens and leverage their exposure to APCs, such as DCs, which is maximized by immunoadjuvant TLR7/8 agonist properties in eliciting robust DC activation at both PC TME and lymph nodes. As proposed in other studies, the IRT-loaded silicasomes display enhanced features when compared to clinically approved Onivyde®, as the lipid shell has enhanced stability and is supported by the MSNP core and allows IRT remote loading and enhanced encapsulation efficiency and drug retention. Furthermore, the increased stability of the final system has shown increased safety profile by minimizing deleterious side effects such as bonne marrow toxicity, hepatotoxicity and damage to the intestinal epithelium [174]. Other applications of silicasome-based technology for improving ICD effect of chemotherapeutic drugs include activated OXA (1,2-diamminocyclohexane platinum(II) (DACHPt) which exerted superior anticancer cytotoxic and ICD effects when compared with free drug, displayed enhanced colloidal stability and pharmacokinetics, and amplified anticancer response in combination with anti-PD-1 antibody [167].

Another interesting strategy was able to combine CT, stroma remodeling and immunomodulatory modalities in hybrid lipid-polymer nanosystem composed of immunostimulatory IL-12 plasmid DNA/polyethyleneimine complexes coated with CAF-targeted aminoethyl anisamide-modified liposomes loaded with lipid-GEM prodrug and JQ1, a BRD4 inhibitor (Fig. 9. A) [165]. First, the system could efficiently target CAFs and induce ECM degradation and enabling infiltration of immune cells for IT, which was boosted by expression of immunostimulatory interleukin IL-12 (Fig. 9. B). The C18 ceramide containing in the liposomes worked as an exosome inducer and stimulated exosome secretion containing lipid prodrug GEM elaidate, as shuttles for PC delivery of GEM. Once inside the PC cells, the prodrug was cleaved by esterase action and GEM was activated to exert cytotoxic activity. *In vivo* results showed promising reduction in tumor growth and enhanced survival, while maintaining body weight (Fig. 9. C-E). This study reveals an elegant strategy to target CAFs and improve chemo-immunotherapy by stroma remodeling and exosome-mediated trafficking of GEM prodrug to PC cells.

Another emergent field of research is CAR-mediated IT, which has revolutionized cancer therapy, particularly blood-related cancers, by instructing immune system to recognize and attack cancer cells with maximized efficacy and specificity. Nonetheless, solid tumors like PC are immune-excluded and the presence of tumor-residing immune cells is very limited, adding up to the additional stroma barrier that impedes further infiltration of effector immune cells and immunotherapeutic action [175]. So far, while CAR-T cells are the main class of CAR-related cell therapy relying on potent cytotoxicity and durable responses [176–178], the field has expanded towards development of CAR-macrophages which bestow improved TME infiltration and immunomodulation activity [179,180], and improved safety and dual cancer cell eradication mechanisms of CAR-NK [181,182] cell therapies bridging CAR technology with the individual attributes of other immune cell types. By taking advantage of silicasome technology, a new study developed *in situ* engineered of tumor-associated macrophages in MUC-expressing PC, with CAR receptor through CAR pDNA-loaded polymeric core and a lipid bilayer containing CD47 inhibitor for improved CAR-macrophage IT [168].

3.2.4. *Lipoprotein-mimicking nanosystems*

Lipoproteins consist of endogenous nano-sized structures with well-defined physiological roles and bearing interesting targeting features [183]. The development of biomimetic systems took inspiration from these circulating nanostructures to develop highly biocompatible, targeted lipoprotein-mimicking systems loaded with drugs for PC intervention [184]. In this regard, a strategy was devised to deliver OXA-furoxan conjugate in lipoprotein-mimicking nanosystem composed of non-PEGylated – DMPC, and PEGylated phospholipids functionalized with stroma-targeted HC8 peptide (DSPE-PEG-HC8) decorated with apolipoprotein A1 (ApoA1) peptide [122]. OXA-furoxan conjugate comprises a functional unit with NO-donor properties, and when activated it can release OXA for cytotoxic activity and consequent depletion of M2 TAMs [122]. ApoA1 decoration enables targeting of TAMs by interacting to the scavenger receptor class B type 1 (SR-B1) in TAMs and C8 peptide endows the system with enhanced TME targeting features. Overall, the system was able to holistically reprogram TME by stroma remodeling, vasculature normalization and improved infiltration of cytotoxic immune cells which could synergize with anti-PD-L1 IT [122]. In the next study, high density lipoprotein (HDL)-mimicking NPs were fabricated composed of GEM-phytanyl prodrug amphiphiles, DMPC and free cholesterol producing liposome emulsion capable of accommodating GEM-phytanyl in the lipid bilayer [104]. Giving that apolipoprotein A2 (ApoA2) is typically present in HDLs and ApoA2 levels in PC patients'

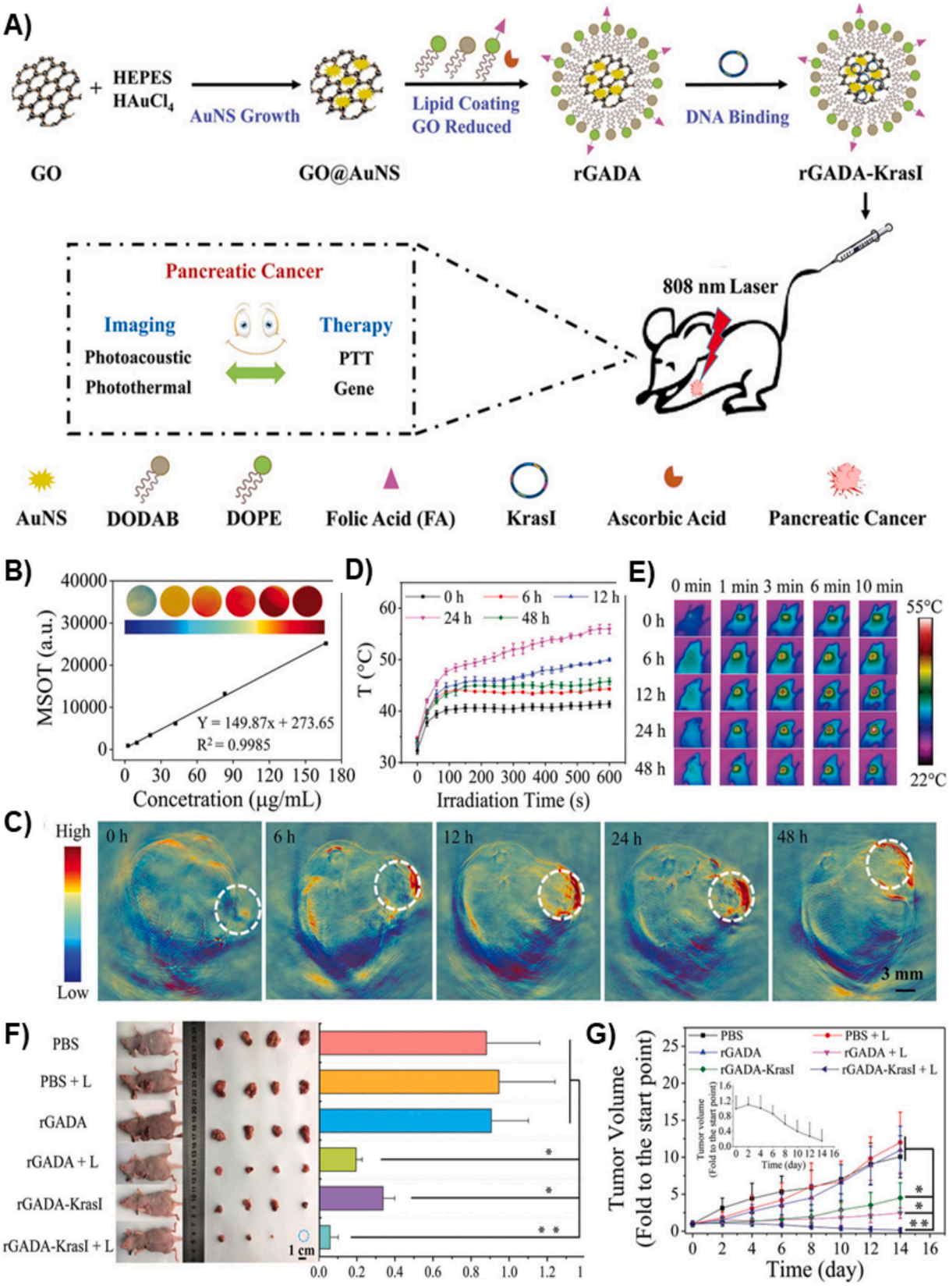

Fig. 7. (A) Schematic illustration of the rGADA system synthesis, and the rGADA/KrasI complexes employed in gene/PTT synergistic therapy and photoacoustic/photothermal dual-modal imaging in PC. (B) Photoacoustic performance for rGADA. (C) *In vivo* PAIs of tumor locations. (D) Tumor temperature curves and (E) infrared thermal images (808 nm laser irradiation, power density of 1.2 W cm^{-2}). (F) Average tumor weight evolution after various treatments. (G) Relative tumor volumes. L means 808 nm laser at power density of 1.2 W cm^{-2}. Adapted with permission from [98]. Copyright John Wiley & Sons (2020). *Abbreviations:* GO, graphene oxide; rGADA, lipid coated graphene oxide/gold nanostar; PTT, photothermal therapy; PAI, photoacoustic imaging.

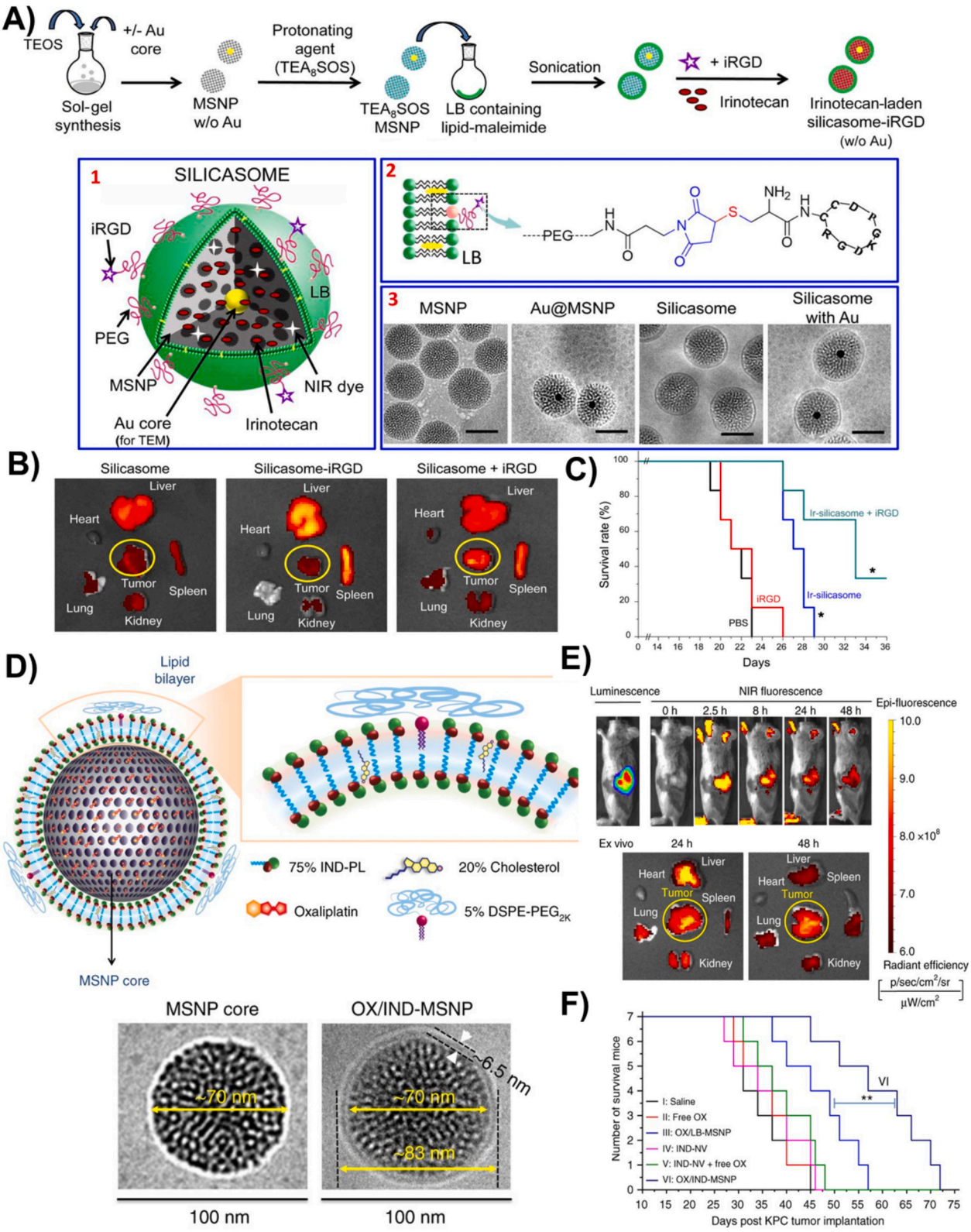

Fig. 8. (A) Schematic illustration of the synthesis and characterization of drug-loaded silicasomes. MSNP cores were synthesized by sol-gel chemistry and further coated with a LB, through sonication. Then, TEA_8SOS mediated remote loading of irinotecan. Box 1: illustration of the silicasome components. Box 2: iRGD peptide conjugation to the LB. Box 3: cryoEM pictures showing the bare particles and the silicasomes, with and without the embedding of approximately 10 nm Au cores (for TEM visualization). Scale bars: 50 nm. (B) *In vivo* performance in KPC-derived orthotopic model. (C) Survival analysis after iRGD coadministration with irinotecan-loaded silicasome. Adapted with permission from [101]. Copyright ASCI (2017). (D) Exploration of a dual OX plus IND co-loaded lipid-bilayer coated mesoporous silica NPs (OX/IND-MSNP) and CryoEM pictures showing a spherical MSNP core coated with a lipid bilayer. (E) Biodistribution of OX/IND-MSNP in orthotopic-implanted KPC tumors in mice. (F) Survival effect of OX/IND-MSNP *vs.* the controls. Adapted with permission from [103]. Copyright Springer Nature (2017). *Abbreviations:* MSNPs, mesoporous silica nanoparticles; iRGD, 9 aminoacid-based peptide; LB, lipid bilayer; NIR, near infrared; OX, oxaliplatin; IND, indoximod.

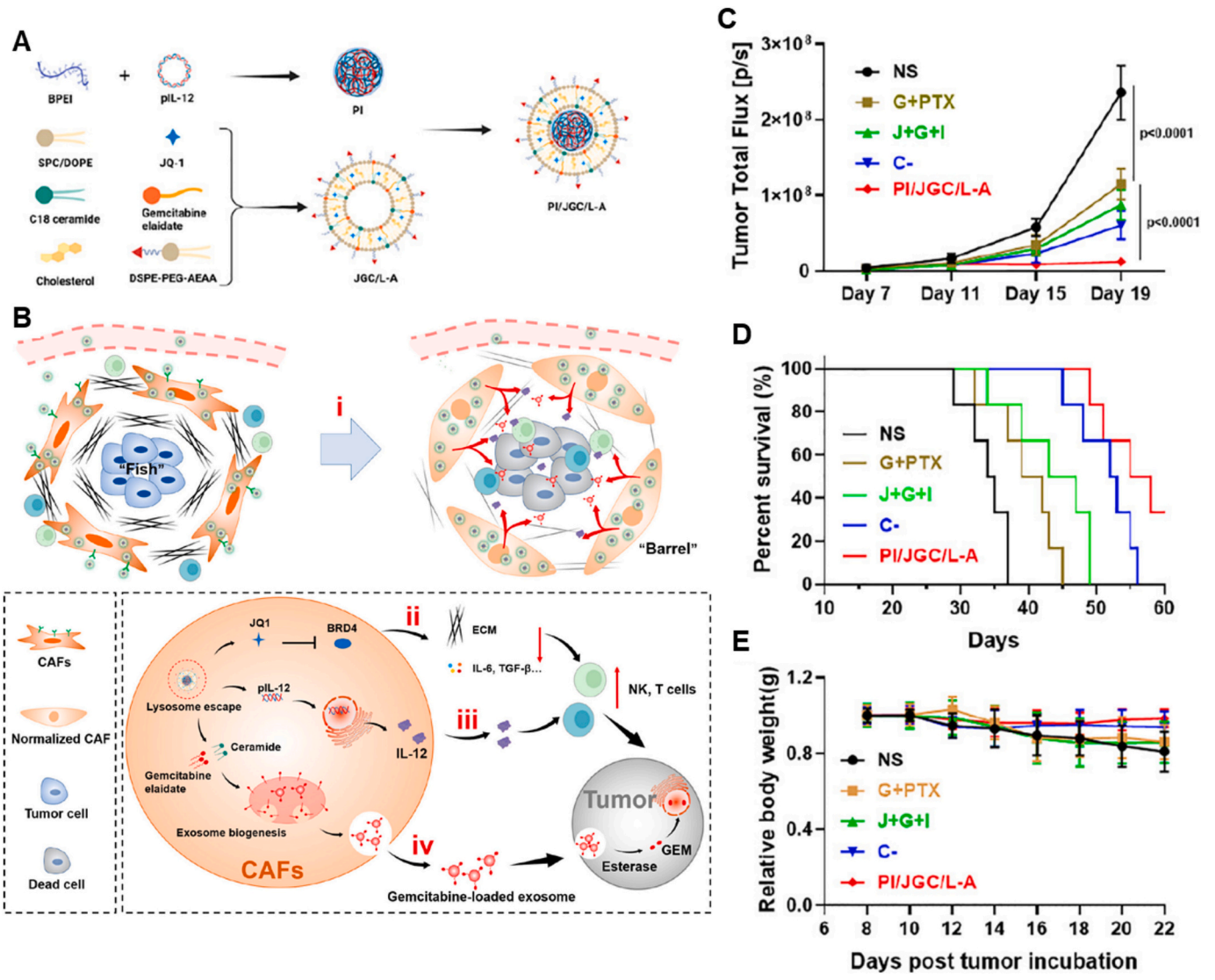

Fig. 9. (A) Schematic illustration of PI/JGC/L-A system. (B) Mechanistic insight of PI/JGC/L-A system. PI/JGC/L-A system enables stroma bypassing and efficient drug delivery to PC cells, improved immune cell infiltration at the tumor site, and potentiates chemo-immunotherapy: i. PI/JGC/L-A targeted CAFs, ii. PI/JGC/L-A normalizes CAFs and depletes collagen deposition and increase immune cell infiltration and viability, iii. PI/JGC/L-A promotes IL-12 release for TME reactivation, iv. PI/JGC/L-A regulates the delivery of gemcitabine to PC through CAF-secreted exosomes. (C) Bioluminescence intensity. (D) Survival curves after administration. (E) Body weight changes in 14 days. Adapted with permission from [165]. Copyright American Chemical Society (2023). *Abbreviations:* PI/JGC/L-A, polyethylenimine/IL-12 plasmid DNA core, coated by liposome loaded with JQ1 inhibitor and gemcitabine elaidate prodrug, further functionalized with AEAA peptide; CAFs, cancer-associated fibroblasts.

plasma have shown to be reduced, ApoA2protein was further mixed with the liposome emulsion to form ApoA2-anchored biomimetic NPs termed sHDLGemA2 for targeted PC intracellular delivery of GEM [104]. The addition of ApoA2 produced more uniform spherical liposomes, contributed to a homogeneous size distribution (PDI ~0.17 decreased to ~0.05) and improved stability. sHDLGemA2 uptake in PC cell was suggested to be an endocytic process mediated by SR-B1 expressed on the surface of PC cells. *In vivo* studies showed that treatment with sHDLGemA2 enabled marked reduction of GEM needed for a substantial decrease in tumor growth (*ca.* 6 % of standard GEM dose), prolonged circulation and controlled GEM release [104]. Although fluorescence intensity of dye-labeled sHDLGemA2 elicited substantial tumor biodistribution for all *in vivo* models tested, significant difference was observed between *in vivo* models as stroma-rich xenografts seemed to benefit less from the treatment when compared to more epithelial-like phenotype xenografts which tend to express more E-cadherin, as tumor growth inhibition was more limited [104].

3.3. Cell membrane-coated nanosystems

The repertoire of cell membranes is diversified regarding function, structure and composition and broadly affects recognition, binding, adhesion and homing of a vast array of cells (Fig. 10) [185]. The intricate network of interactions established between cells and their exterior microenvironment is governed by cell-cell interactions and cell-tissue interactions (*e.g.* cell-ECM) conveyed by cell membrane surface-expressed molecules (Table 6). For instance, by promoting cell-cell contact and adhesion by establishment of well-known homophylic and heterophilic interactions, cells can form cohesive and stabilized adhesive structures with other cells and tissues and underpin physiological and pathological processes [186,187].

Cellular adhesion molecules (CAMs) are constitutively expressed in the surface of cell membranes and include a vast repertoire of immunoglobulin superfamily (IgSF) members, integrins, selectins, cadherins and CD44 family, responsible for vast array of intracellular and extracellular signaling processes [186]. These molecules can bind to certain

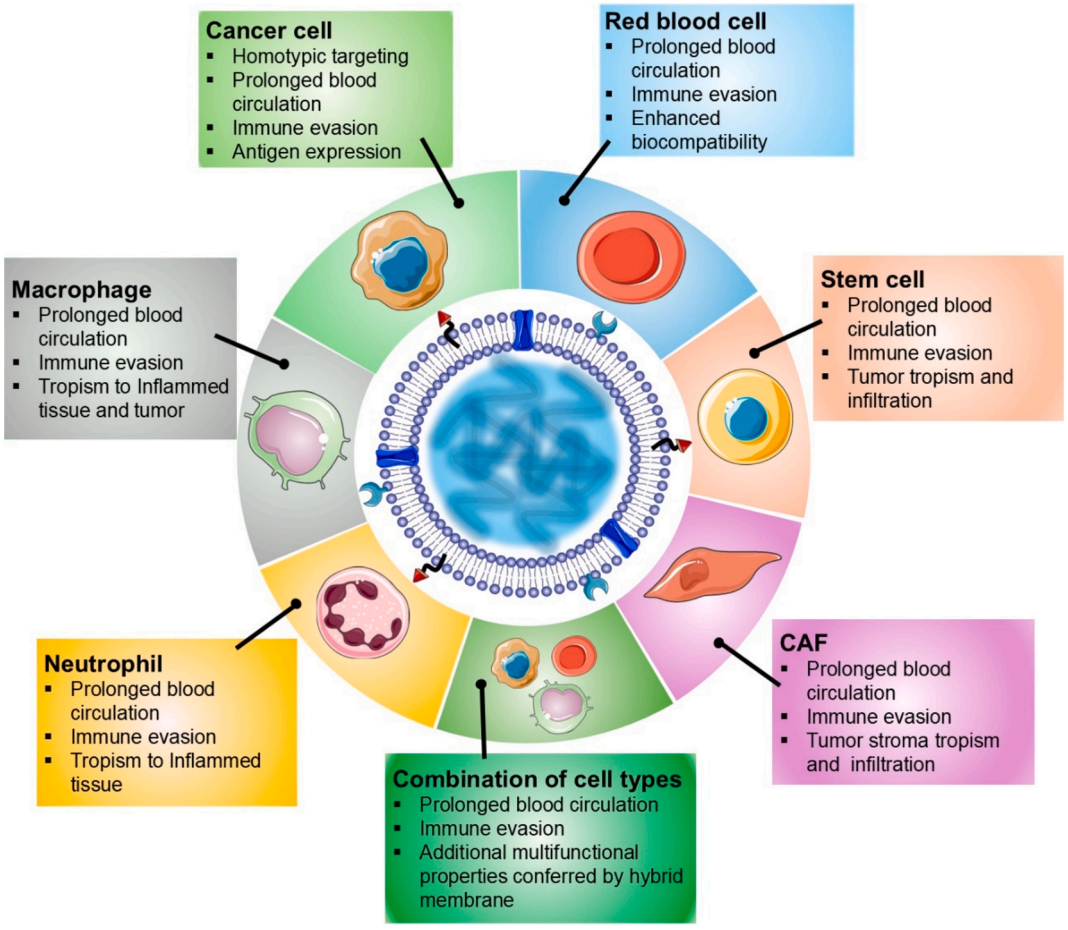

Fig. 10. General features imparted by cell membranes used to engineer cell membrane-coated nanosystems.

ligands, namely ECM, soluble ligands and membrane-expressed and enable cell-cell adhesion [186,206]. Most widely known IgSF members include major histocompatibility complex (MHC) I and II complex, intercellular adhesion molecules (ICAMs), vascular cellular adhesion molecules (VCAMs), and T cell receptor molecules (TCMs).

Selectins (CD62) are a group of structurally-related transmembrane glycoproteins involved in calcium-dependent leukocyte-endothelial cell adhesion processes and display particular relevance in what concerns leukocyte trafficking and migration to tissues [206]. Of interest, expression of selectin subgroups varies depending on cell types, namely platelet- and endothelial cell-expressed P-selectins (CD62P), E-selectins (CD62E) expressed on endothelial cells and L-selectins (CD62L) typically expressed on leukocytes [207]. Selectins intervene at an early stage of the leukocyte migration cascade as they initiate tethering and rolling of leucocytes through surface of endothelial cell of microvasculature by leukocyte-endothelial cell interactions (L-selectin-sLeX) and endothelial cell-leukocyte (P−/E-selectin- sLeX) [186] [206,207]. Natural selectin binding ligands are terminal carbohydrate residues typically consisting of tetrasaccharide sialyl-Lewis^{x} (sLeX also known as CD15s) attached to glycan chains of glycoproteins present on endothelial and leukocytes and interact with N-terminal lectin domain of selectins [207–209]. Specifically, P-Selectin Glycoprotein Ligand-1 (PSGL-1) is the typical ligand for P-selectin and E-selectin and is expressed on leukocytes [209]. Additionally, E-selectin binds to cutaneous lymphocyte-associated antigen (CLA), E-selectin ligand 1 (ESL-1), CD43, and CD44 [207]. L-selectin binds to 6-sulfo-modified sLeX attached on core glycan structure of cell surface glycoproteins Glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1), CD34 and mucosal vascular addressing cell adhesion molecule 1 (MAdCAM-1) [209]. Additionally, platelets express P-selectin which can interact with transmembrane glycoprotein CD44 on cancer cells surface [210].

β2-integrins are the main class of integrins expressed by leukocytes and include lymphocyte function-associated antigen 1 (LFA-1), which presents a narrower binding repertoire resumed for instance to ICAM-1-5 and JAM-1 family members, when compared to macrophage-1 (Mac-1) which may bind to ICAM-1-4, fibrinogen and fibronectin, to name a few. Interaction between endothelial ligands (ICAM-1, VCAN-1) and respective leukocyte-expressed integrins (LFA-1 and VLA-4) promote strong leukocyte-endothelium interaction and firm adhesion. Hence, they support rolling processes and mediate strong adhesion to endothelium surface and favor transmigration to surrounding tissues [208].

Cadherins, an abbreviation for “calcium-dependent adherent proteins” as they are able to bind to specific ligands in a calcium-dependent fashion, play a pivotal role in cell-cell contact formation and adhesion processes mainly *via* a homophilic interaction [186]. Adhesion tension by lowering interfacial tension at cell-cell contact surface [211]. Epithelial cadherin (E-cadherin) displays cell-adhesive properties, namely homotypic cell-cell adhesion, neural cadherin (N-cadherin) and vascular endothelial cadherin (VE-cadherin). Cadherins also promote intracellular adhesion *via* formation of *adherens junctions* [212].

CD44 belongs to the lymphocytes homing receptor family and is a ubiquitous cell surface receptor for several biological ligands including hyaluronic acid, matrix metalloproteinases and collagens, mainly present in the ECM of tumor tissues. Studies have shown CD44 is widely expressed at the surface of cancer cells and play an active role on cancer cells migration, invasion and metastasis on account of its adhesive properties [213]. Several CD44 variants have been described and impact differently cancer proliferation and metastasis.

Table 6
Typical surface markers present on cell membranes from distinct sources and their role on biointerfacing and biomimetic nanosystems features.

Cell membrane	Molecule	Function	Ref.
RBC	CD47	• "don't eat me signal" • Interaction with SIRPα • Immune escape • Prolonged blood circulation	[134]
	glycophorin A	• ↓ immune recognition of RBC	[188]
	Spectrin, Ankyrin, band 3 protein	• Integrity, flexibility and stability of the RBC cell membrane	[188]
Cancer cell	CD47	• "don't eat me signal" • Interaction with SIRPα • Immune escape • Prolonged blood circulation	[88,134,189]
	Cadherins	• Cell adhesion • Homotypic adhesion	[88,189]
	Integrins	• Cell adhesion • Homotypic adhesion	[88,190]
	Selectins	• Cell adhesion • Homotypic adhesion	[88,190]
	CD44	• Cell adhesion • Homotypic adhesion	[88,190]
	Mucins	• Cell adhesion • Homotypic adhesion	[190]
	HER2, EGFR	• Cancer cell targeting	[191]
	EpCAM	• Cancer cell targeting	[191]
	Thomsen–Friedenreich antigen	• Homotypic adhesion and targeting	[88,189]
Macrophage	Integrin $\alpha_4\beta_1$	• Cell adhesion • Binds to VCAM-1 on cancer cells	[192,193]
	MAC-1	• Binds to tumor tissue	[194]
	LFA-1	• Binding to ICAM-1 • Targeting to endothelium and inflamed tissue	[89]
	PSGL-1	• Targeting to E-selectin, L-selectin and P-selectin • Targeting to endothelium	[89,195]
	L-selectin	• Binds to sialyl Lewis X (sLe^x) • Binds to PSGL-1 on endothelial cells	[89,195]
	CD47	• Inhibit phagocytosis	[134]
	CCR2	• Monocyte recruitment	[196]
	CD11a/b/c	• Cell adhesion	[197]
	MHC I and II	• Exposure of tumor antigens	[198]
	CCL2 secretion	• Binding to tumor cells	[192]
Neutrophil	LFA-1	• Binding to ICAM-1 • Targeting to endothelium and inflamed tissue	[199,200]
	Integrin β1	• Binding to VCAM-1	[200]
	CD44	• Binding to L-selectin	[200]
Stem cells	Chemokin receptors	• Tropism to inflamed and tumor tissues	[87,201,202]
	Interleukin receptors	• Targeting to inflamed tissues	[202]
	P-selectin	• VCAM-1/VLA-4	[203]
	CD47	• Inhibit phagocytosis	[87]
	ICAM-1, ICAM-2, CD166, VCAM-1, Integrins	• Tropism to inflamed and tumor tissues	[87,202]
Platelet	Glycoprotein Ib-IX-V Complex	• Binding to damaged blood vessels	[190]
	Integrin $\alpha_{IIb}\beta_3$	• Binding to damaged blood vessels	[190]
	P-selectin	• Targeting to damaged blood vessels and tissue • Binding to CD44 on tumor cells	[204,205]
	CD55, CD59	• Suppression of complement system	[204]

Galectin-3 (Gal-3) β-galactoside-binding glycoprotein belonging to lectin family known to regulate cell adhesion processes and is expressed either intracellularly, as transmembrane glycoprotein and in its secreted form [214]. For example, Gal-3 is frequently overexpressed in colorectal cancer and is able to bind to epithelial glycoproteins called mucins, such as secreted gel-forming mucin MUC2 [215]. Also interestingly is the ability of Gal-3 to interact with Thomsen-Friedenreich (TF) antigen, which has been pointed out to drive cancer progression and metastasis [216]. TF antigen represents one of the most studied tumor-associated carbohydrate antigens and is often overexpressed and exposed in cell membrane glycoproteins in cancer context including MUC1, a family of transmembrane mucin proteins [216]. Interaction of Gal-3 with MUC1 induces clustering and homotypic adhesion and aggregation of cancer cells and adhesion to endothelium facilitating metastatic process [216,217]. The impact of surface repertoire of cell membrane-based nanosystems on tissue targeting has been reviewed elsewhere in more detail [218].

In the particular context of cancer, overexpression of CAMs favors highly-specific homologous (homotypic) adhesions between cancer cells [219]. This has led researchers to develop cancer-targeted drug delivery approaches relying on homotypic targeting, based on the ability of cancer cells to interact with each other with high specificity and selectivity *in a* ligand-receptor fashion (the ligand and the receptor can be different or the same molecules, the latter may occur in the case of cadherin-cadherin homotypic interaction). Examples of PC-targeted cell membrane-coated nanosystems are summarized in Table 7.

3.3.1. *Neutrophil cell membrane-coated nanosystems*

Neutrophils represent the most abundant white blood cells in the body and their membranes can be extracted to build neutrophil cell membrane-coated nanosystems with the enhanced ability to target inflamed tissue and vasculature, which facilitates penetration in the TME [226,227]. The link between inflammation and PC was explored in a recent study comprising cell membrane coating technology for biomimicry and circumvention of PC-associated barriers towards PC-targeted compound delivery [110]. In this study PEG-PLGA NPs loaded with celastrol, a plant-derived pentacyclic triterpenoid bearing anti-inflammatory properties, were coated with neutrophil membrane

(thickness 10–20 nm) able to recapitulate the biofunctionality of native membranes towards neutrophil-like properties (Fig. 11. A) [110]. This strategy has been suggested to enable targeting specificity to inflamed/tumor tissues on account of natural ability of neutrophils to be recruited as inflammation mediators and access inflamed tissues. Surface repertoire of native neutrophil membrane was successfully transferred into the membrane coatings, including proteins such as fibrinogen, actin, histone, tubulin and vinculin [110]. Most of the transferred surface proteins are of structural nature or mediate adhesion, signaling, and transport in native neutrophils. Interestingly, the neutrophil membrane-coated NP showed not only enhanced targeting to PC cells (*ca.* 4-fold higher) but also to endothelial cells when compared to non-coated NPs, which may attest dual tumor- and inflammation-targeting abilities conferred by the coating accompanied with reduced immune system clearance. Results showed enhanced *in vivo* tumor accumulation and anticancer properties, in Panc-2 ectopic xenografts and GFP-Panc-2 orthotopic mice models (Fig. 11. B-G) [110]. The neutrophil cell membrane-coated nanosystem was able to extravasate blood vessels and surpass blood–pancreas barrier achieving anti-inflammatory response evidenced by downregulation of inflammatory mediators such as IL-6, IL-1β as well as cancer cell proliferation and survival proteins including NF-κB [110]. In another study, GEM was loaded in liposomes modified with neutrophil cell membrane and association with nanosecond pulsed electric field showed promising results for PC therapeutics [111].

3.3.2. Macrophage cell membrane-coated nanosystems

Macrophages are key mediators of immune response exerting relevant anticancer effects in the TME. Macrophage membrane-coated nanosystems produced after combination of macrophage cell membranes and NP cores retain surface repertoire of native cells and enable prolonged circulation half-life of drugs and NP cores and enhanced tropism to inflamed tissue (*e.g.* TME cells) and deep tumor penetration [89]. So far, two strategies have been devised to target PC with macrophage membrane-coated nanosystems, both loaded with anticancer drug GEM [105,106]. One strategy developed GEM prodrugs (GEM coupled to fatty acid chain) to improve GEM stability, solubility, and release profiles [106]. Then, GEM prodrug was loaded in poly (ethylene glycol)-b-poly(2-(diisopropylamino) ethyl methacrylate) (PEG-PDPA) micelles assembling GEM-loaded PEG-PDPA micelles, further coated with macrophage membrane (surface markers CD11b, CCR2, Na/K-ATPase were detected) and tested in combination with free anti-PD-L1 antibodies (Fig. 12. A-C). The combination of IT with the GEM-loaded macrophage membrane-coated system could substantially improve tumor survival in PC bearing mice models of disease (Fig. 12. D). Another recent strategy encompassed wrapping GEM-loaded poly lactic acid-*co*-glycolic acid (PLGA) NPs cores with functional macrophage cell membranes to achieve improved tumor drug delivery and accumulation [105]. The macrophage membrane was 8–10 nm thick and conserved typical surface repertoire including CD309, MDR1 and CD135. The macrophage cell membrane-coated GEM-loaded NPs co-administered intravenously with epidermal growth factor receptor (EGFR) inhibitor erlotinib were able to target concurrently two signaling pathways – PI3K/AKT/mTOR and Ras/Raf/MEK/ERK – and showed a substantial synergistic tumor growth inhibition on PANC-1 xenograft tumor model, when compared to free GEM and isolated administration of the biomimetic NPs (Fig. 12. E). An additional study also explored hybrid liposome-macrophage cell membrane decorated with LFC131 peptide for PC overexpressed C–X–C motif chemokine receptor 4 (CXCR4) targeted delivery [220]. The hybrid membrane served as biomimetic coating for glutamine-fructose-6-phosphate aminotransferase 1 (GFAT1) siRNA-encapsulated calcium phosphate NPs aimed at stroma decompression by decreasing HA production and enhance delivery of Doxil®, a commercial doxorubicin liposome formulation to PC. Combination of PDT with IT by employing macrophage cell membrane-coated NPs is also another exciting area of research that enables PC TME remodeling from immunosuppressed state to immunoactivated state. For instance, through a concerted mechanism established between maximized reactive oxygen species (ROS) and reactive nitrogen species production (RNS) and poly-L-arginine as nitric oxide (NO) donor for stroma normalization, the efficacy of PD-L1 siRNA IT can be significantly augmented [221].

3.3.3. Pancreatic cancer cell membrane-coated nanosystems

The homotypic targeting properties of PC cell membranes have been explored to engineerNP cores for improved PC-targeted therapies and is considered an attractive strategy to improve PC therapeutics. An interesting study showed mesoporous silica nanorods and mesoporous silica nanospheres coated either with natural PC-derived cell membrane or a synthetic lipid bilayer [124]. The coating process increased the size of the formulations by 10 nm (130 nm) and conferred a nearly neutral charge by shielding the negatively charged surface of mesoporous silica NPs. The PC cell membrane-coated NPs showed the lowest protein corona formation indicative of less interaction and binding to serum proteins when compared to synthetic lipid bilayer-coated NPs and bare NPs, as well as superior immune escape properties from phagocytic cells. Interestingly, nanorods were preferentially internalized by BxPC-3 cells in detriment of nanospheres and deliver anticancer agent doxorubicin to the nuclear vicinity, namely endoplasmic reticulum. This may be intimately connected to the internalization mechanism of nanorods, which was mediated by caveolin instead of clathrin, therefore avoiding endolysosomal compartment and minimizing lysosome-mediated degradation. Doxorubicin-loaded PC cell membrane-coated nanorods elicited significantly higher doxorubicin accumulation in the nucleus of BxPC-3 cells as opposed to synthetic lipid bilayer-coated nanorods or cell membrane- coated nanospheres (3-fold and 4-fold higher, respectively). The PC cell membrane-coated nanorods also exhibited enhanced penetration and diffusion on BxPC-3/HPSC multicellular spheroid model as an approach to mimic *in vivo* conditions of PC TME and the strongest anticancer activity in BxPC-3/PSC hybrid tumor-bearing subcutaneous mice xenografts [124].

To improve bioavailability and decrease systemic toxicity of FOLFIRINOX® regimen, 5-FU, IRT and OXA – three of the four components of FOLFIRINOX® – were co-loaded in PLGA NPs coated with BxPC-3 cell membranes (Fig. 13. A, B) [129]. The system was able to target PC tumor and improve delivery of FOLFIRINOX® and evidenced superior tumor inhibition profile as well as superior survival rates when compared to non-coated or free FOLFIRINOX® systems (Fig. 13. C, D), after intravenous administration in mice models of the disease (Fig. 13. E) [129]. Acetoaminophen was loaded in nanogels coated with Panc2 cell membrane for prostaglandin E2 inhibition and activation of DCs and NK cells, hence unleashing the anticancer activity mediated by immune cells, combined with homologous targeting features conferred by the PC cell membrane (Fig. 13. F, G) [107]. *In vivo* results showed the best tumor reduction for the group treated with the Panc2 cell membrane-coated nanogel in combination with free anti-PD-L1.

Other studies employing PC cell membrane coating include (1) dual targeting of PC cells and macrophages, by tumor associated macrophage-targeted peptide-decorated KPC cell membrane-coated and GEM-loaded PLGA NPs, explored in combination with free anti-PD-L1 (Fig. 13. H) [125]; (2) PANC-2 cell membrane coated ultra-thin tungsten disulfide nanosheets to reduce tumor interstitial pressure by water splitting and oxygen release, which could improve hyperthermia-mediated cell death by enhanced ROS production by O2 conversion [228]; (3) improving stroma penetration and tumor targeting by collagenase-decorated BxPC-3 cell membrane-coated gold nanocages loaded with doxorubicin for enhanced CT of PC relying on the improved stroma penetration by collagenase-dependent ECM degradation, and to the homotypic targeting features conferred by the cell membrane [126]; and improved stroma penetration of collagenase-functionalized MSNs loaded with copper and disulfiram for deep tumor penetration and cuproptosis of PC and copper-mediated T1-weighted magnetic

Table 7
Examples of cell membrane-coated nanosystems for advanced PC-targeted therapies.

Nanosystem	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
Neutrophil membrane-coated nanosystems								
PEG-PLGA NPs	CLT	–	167	−15	i.v., formulation equivalent to 1 mg/kg CLT	PANC-2 cells Ectopic and orthotopic PANC-2 mice xenografts	- ↑ cellular uptake by tumor cells - ↑ antitumor efficacy	[110]
Liposomes	GEM	–	~175	~ −16	i.v., formulation, 4 times (3,6,9,12 days), nsPEF at day 0	PANC-2 cells PANC-2-bearing mice	- ↑ tumor accumulation - ↑ immune escape - Best tumor growth reduction for group receiving a combination with nsPEF	[111]
Macrophage membrane-coated nanosystems								
PLGA NPs	GEM	–	192	−18	i.v., 5 mg/Kg, every 2 days, 6 doses	PANC-1 cells Subcutaneous PANC-1 xenografts	- ↓ uptake by the immune system - ↑ circulation half-life - ↑ tumor biodistribution - ↓ tumor weight especially when combined with ELT	[105]
PEG-PDPA micelles	GEM-lipid prodrug	–	94	−6	i.v. injection 5.0 mg/kg of GEM 5 times (0,2,4,6,8 day) combined with anti-PD-L1 (1,3,5,7,9 day)	PANC-2-bearing mice	- GEM prodrug derivative - ↓ T cell exhaustion - ↑ T cell infiltration - ↑ anticancer activity in combination with anti-PD-L1 antibodies	[106]
Calcium Phosphate NPs	GFAT1 siRNA	LFC131	122	19	i.v. injection siGFAT1, 0.75 mg/kg, and Doxil® 1.5 mg/mL	Subcutaneous BxPC-3/NIH 3T3 xenografts and orthotopic PANC-1-luc-3/NIH 3T3	- fusion of liposome with macrophage cell membrane - LFC131 peptide modification for enhanced cellular uptake - ↑ stroma remodeling and vasculature decompression by GFAT1 silencing and decreased HA production - ↑ anticancer activity in combination with Doxil®	[220]
PPA-PArg	PD-L1 siRNA, PPA	’	146	−14	i.v. injection, PPA 1 mg/kg + laser irradiation 12 h later (650 nm, 8 mW/cm^2, for 2 min)	Subcutaneous PANC-2 tumor-bearing mice	- photosensitizer pyropheosylchlorine-α (PPA) conjugation to poly-l-arginine (PArg) - M1 macrophage cell membrane coating containing integrin proteins α_4 and β_1 - ↑ production of ROS and reactive nitrogen species (RNS) - PArg-mediated NO release - ↑ TME reprogramming and ECM degradation - ↑ remodeling of immunosuppressed M2 macrophages - ↑ PD-L1 IT - ↑ anticancer activity in combination with Doxil®	[221]
PC cell membrane-coated nanosystems								
Mesoporous silica nanorods	DOX	–	133	−21	i.v., 2.5 mg/kg DOX in coated nanorods/day for 19 days	BxPC-3 cells Simulated ECM hydrogel BxPC-3/HPSC MCS Hybrid BxPC-3/HPSC subcutaneous mice model	- Homotypic targeting and uptake by PC cells - ↑ ECM and MCS penetration - Endoplasmic reticulum targeting - ↑ DOX delivery to the PC cell nucleus - ↓tumor growth	[124]
Nanogels	AMP	–	128	−21	4 times i.v. injection 2.5 mg/kg (0,2,4,6 day) combined with free i.p. anti-PD-L1 (2,6 day)	PANC-2 mice-bearing xenografts	- ↑ activated CTLs and NKs - Efficient DC maturation - ↑ memory T cells - ↑ tumor growth reduction when combined with anti-PD-L1 - Efficient postsurgical PC recurrence prevention	[107]
PLGA NPs	GEM	M2pep	118	−22	4 times i.v. injection (0,3,6,9 day) combined with free i.p. anti-PD-L1 (1,4,7,10 day)	KPC tumor-bearing mice	- Vaccine-like properties by TAA by the PC membrane - Macrophage targeting - ↓ immunosuppressive TME	[125]

(*continued on next page*)

Table 7 (*continued*)

Nanosystem	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
Gold nanocages	DOX	Collagenase	104	−25	3 times i.v. injection 10 mg/kg (0,2,4 day) combined with NIR irradiation (1,3,5 day)	BxPC−3 tumor-bearing mice	- ↑ anticancer activity of GEM in combination with anti-PD-L1 - Expression of CD47, EpCAM, and N-cadherin surface markers of PC membrane - Stroma targeting and remodeling - ↑ tumor penetration - Combined PTT, PDT and chemotherapy - Imaging properties	[126]
PLGA NPs	5-FU + IR + OXA	–	149	- -3	i.v. injection every 2 days, 10 times	BxPC-3 tumor-bearing mice	- PEGylated cell membrane - EpCAM, MUC1, CD47 markers expressed at the surface - ↓ systemic toxicity - ↑ immune escape and circulation - ↑ tumor targeting	[129]
Gold nanocages	NO donor + GEM	–	125	- −10	i.v. injection 5.0 mg/kg of GEM equivalent and gold nanocages 15 mg/kg (0,3,6 day) combined with NIR irradiation (1,4,7 day)	SW1990 tumor-bearing mice and PDXs	- GSH-responsive GEM release - ROS-mediated activation of NO donor - ↑ GEM penetration due to NO-mediated vasodilation - stroma vasculature remodeling - photothermal therapy in combination with chemotherapy - photoacoustic imaging	[127]
UCNP-$Zn_xMn_{1-x}S$ NPs	–	–	179	- −18	10 mg/kg of NP, followed by irradiation	BxPC-3 tumor-bearing mice	- ↑ oxidative stress - ↓ GSH overexpression - ↑ sensitivity of PC to oxidative stress - ↑ tumor accumulation	[130]
DSPE-PEG NPs	TPC (NIR-II emissive dye)	-	6	- −53	i.v. 100 μL, 1.0 mg/mL TPC NPs 10 min irradiation 808 nm laser (0.33 and 0.75 W/cm^2)	PANC-2 mice-bearing xenografts	- ↑ PDT, NIR-II imaging & therapy - Significant photothermal conversion and NIR-II emission - Targeted bioimaging - ↑ Targeting and biocompatibility on account of PC cell membrane	[131]
MSNs	DSF + Cu^{2+}	DSPE-collagenase	~40	–	i.v. 10 mg/kg of NP, 3 times, every other day	BxPC-3 tumor-bearing mice	- Co-delivery of Cu^{2+} and disulfiram for cuproptosis - Collagenase-mediated ECM degradation - ↓ matrix stiffness and ↑ drug accumulation - Homologous targeting to PC cells - Cu-mediated MRI and theranostics	[128]
RBC membrane-coated nanosystems								
Gold nanorods	Free CPM	–	–	−18	Oral administration of CPM 10 mg/mL (50 mg/kg)/day for 3 weeks +150 μL of coated nanorods (2.5 mg/mL gold content)	Capan-2 cells Capan-2-bearing subcutaneous xenografts	- ↑ *in vivo* tumor perfusion after CPM treatment - ↑ *in vivo* photoacoustic signal - ↑ tumor accumulation after CPM treatment (1.8-fold) - ↑ PTT activity and tumor growth inhibition rates (*ca.* 80 % for laser + CPM group *vs. ca.* 14 % for laser group)	[108]
PEG-PLGA NPs	DOX + RA	FnBPA5	95	−25	i.v. injection (~ 2 mg/kg DOX) every 3 days for 3 times	PANC-2 (subcutaneous and orthotopic)	- Stroma targeting - Stroma remodeling - ↑ stroma penetration of DOX ↑ DOX activity	[123]
MOFs	ICG	–	122	−4	i.v. injection + laser irradiation (808 nm, 1 W/cm^2)	PANC-2 (subcutaneous)	- Prolonged blood circulation - Effective ICG release in the acidic TME - ↑ photothermal therapy	[222]
PLGA NPs	CPM	–	66	−26	i.v. injection 5 mg/kg CPM every day for 18 days	Capan-2 (subcutaneous)	- Prolonged blood circulation - Enhanced biocompatibility - PC stroma remodeling - ↑ tumor perfusion	[223]

(*continued on next page*)

Table 7 (*continued*)

Nanosystem	Drug	Targeting	Size (nm)	ZP (mV)	Dose	Model	Findings	Ref
	PTX	–	86	−25	i.v. injection 6 mg/kg PTX every three days (14th–26th)		- ↑ PTX delivery to PC and improved anticancer activity	
Stem cell membrane-coated nanosystems								
PLGA NPs	DOX	–	~150	~ −1	i.p. injection, 5 mg/kg DOX, every other day during 12 days	PANC-1 tumor-bearing mice	- ↑ targeting to PC cells - ↑ chemotherapy delivery - ↓ tumor growth - CD90 marker expressed at the surface of membrane	[109]
Cancer-associated fibroblast membrane-coated nanosystems								
MSNs	NNMT siRNA	–	137	−17	i.v. injection, 1 nmol siRNA, in association with GEM, 25 mg/kg	PANC-2 tumor-bearing mice	- ↑ targeting to PC stroma - CAF metabolic reprogramming - ↑ GEM delivery (in 4T1 membrane-coated GEM MSNs) - ↑ cytotoxic T cell infiltration	[112]
Liposomes	JQ1 + Pirfenidone	TAT	156	~ −33	i.v. injection, 10 mg/kg JQ1 and 10 mg/kg pirfenidone, every 2 days, 7 times	MT5-luc + NIH 3T3 tumor-bearing mice	- CAF-targeting homotypic mechanism - ↑ tumor penetration by TAT - stroma remodeling - ↑ JQ1 delivery	[224]
Mesoporous polydopamine NPs	FeCO + Losartan	PTP	126	−136	i.v. injection, 200 mg/mL, 0.2 mL days 13, 16, 19, 22	Subcutaneous PANC-1/NIH 3T3 mice model	- Double targeting mechanism (CAFs and PC) - PTP-mediated PC targeting - losartan-mediated ECM degradation and ↑ tumor penetration - CO-mediated anticancer activity - ↑ tumor growth inhibition	[225]
Hybrid cell membrane-coated nanosystems								
β-cyclodextrin-PEI-ss-GEM	GEM + ERL + IRAK4 siRNA	–	200	−16	i.v. injection, 2 mg/kg Er and 2 mg/kg GEM, 1/week for 2 weeks (SW1990 model) and 1/week for 5 weeks (PDX)	SW1990 tumor-bearing mice, PDX	- GSH-responsive GEM release - homotypic targeting conferred by cancer cell membrane - immune escape features conferred by macrophage cell membrane - ↓ fibrotic stroma, ↑ stroma remodeling - ↑ survival percent when compared to free drug or non-coated system - ↓ metastasis when compared to free drug or non-coated system	[132]
Cationic MSNs	DOX + Hyaluronidase	–	~250	−20	i.v. injection, 5.0 mg/kg DOX, 3 times, day interval	PANC-2 tumor-bearing mice	- pH-responsive liposome coating on MSNs - ↑ targeting features conferred by cancer cell membrane - immune escape features conferred by RBC membrane - ↑ stroma permeation by hyaluronidase - ↑ tumor growth inhibition when compared to uncoated, sole-RBC coated or sole DOX-loaded hybrid coated group	[133]

Abbreviations: ZP, zeta potential; PEG-PLGA, polyethylene glycol–poly lactic acid-*co*-glycolic acid; NPs, NPs; CLT, celastrol; GEM, gemcitabine; i.v., intravenous; nsPEF, nanosecond pulsed electric field; ELT, erlotinib; PEG-PDPA, poly (ethylene glycol)-b-poly(2-(diisopropylamino) ethyl methacrylate); siGFAT1, glutamine-fructose-6-phosphate aminotransferase 1 siRNA; LFC131, CXCR4 ligand; PD L1, programmed cell death ligand 1; PPA-PArg, pyropheophorbide-a-poly-l-arginine; PC, pancreatic cancer; DOX, doxorubicin; MCS, Multicellular spheroid model; HPSC, Pancreatic cancer stellate cells; ECM, extracellular matrix; AMP, acetaminophen; DC, dendritic cell; NK, natural killer cell; CTL, cytotoxic T lymphocyte; i.p., intraperitoneal; TAA, tumor-associated antigens; TME, tumor microenvironment; PTT, photothermal therapy; PDT, photodynamic therapy; 5-FU, 5-fluoracil; IRT, irinotecan; OXA, oxaliplatin; NO, nitric oxide; UCNP, upconversion nanoparticles; CPM, cyclopamine; RA, retinoic acid; NNMT, Nicotinamide *N*-methyltransferase; CAF, cancer-associated fibroblast; PEI, polyethyleneimine; IRAK4, Interleukin-1 receptor-associated kinase 4; MSN, mesoporous silica NPs; PDX, patient-derived xenografts; GSH, glutathione; RBC, red blood cell; FeCO, iron carbonyl; PTP, plectin-1 targeted peptide.

resonance imaging (MRI) [128]; (4) improve chemosensitivity of PC by MIA PaCa-2 cell membrane-coated PLGA/TPGS NPs loaded with bufalin, which could display Gal-3 and EpCAM surface markers for homotypic targeting, with the ability to decrease chemoresistance in PC and improve CT activity [229]; (5) double immunoactivation and stroma remodeling by encapsulating SHH inhibitor in PANC-2 cell membrane nanovesicles, which served as coating to transcription factor SRY-Box Transcription Factor 9 (SOX9) siRNA-complexed dendrimeric cores, in

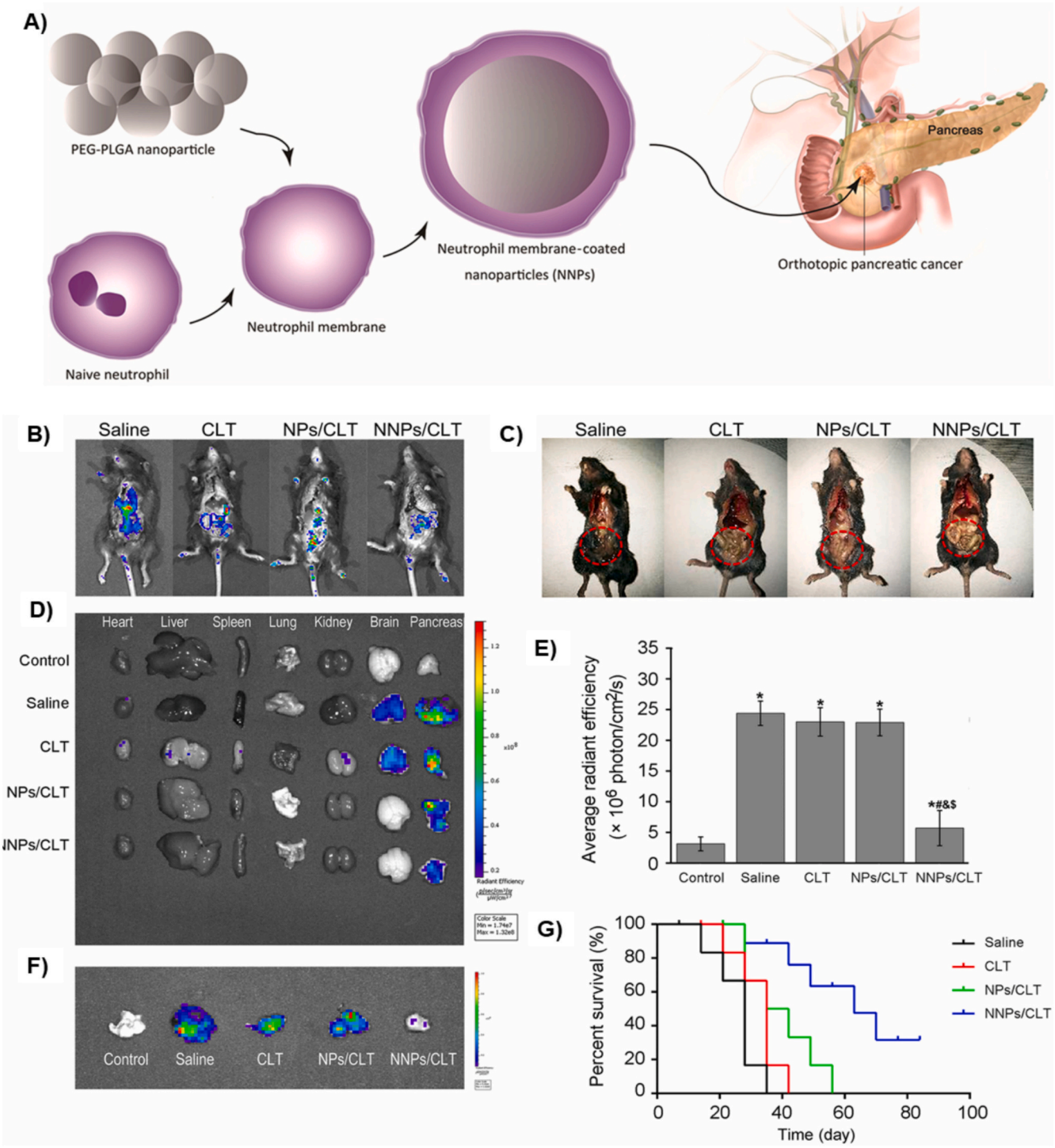

Fig. 11. (A) Schematic illustration of the neutrophil membrane-coated NPs for targeted drug delivery to PC. (B-G) *In vivo* antitumor efficacy in GFP-Panc-2 orthotopic tumor model: (B) Whole-body fluorescence imaging; (C) Disease conditions after treatment; (D) Fluorescence images of vital organs and pancreas; (E) Fluorescent images of tumor-bearing pancreas; (F) Semiquantitative analysis of fluorescence intensity of the pancreas. (G) Survival analysis. Adapted with permission from [110]. Copyright Elsevier (2019). *Abbreviations:* NPs, nanoparticles; CLT, celastrol.

order to reactivate immune system activity in the TME by immunosuppressor cells inhibition and improve T cell recruitment and accumulation, aided by improved stroma permeability [230]; (6) maximize uptake of Nab-PTX, in which hybrid liposome-MiaPaCa-2 cell membranes (with Na+/K + -ATPase and Gal-3 expression) are employed to coat calcium-phosphate NP cores containing autophagy protein 5 siRNA, aimed at autophagy inhibition and enhanced micropinocytosis, thus facilitating Nab-PTX uptake and therapeutic activity [231]; (7) double targeting of macrophages and PC cells achieved by preparing anti-CD40, anti-Claudin 18.2 single chain variable fragments (scFv) KPC cell membrane-coated PLGA NPs as nanoengagers for macrophage activation and PC targeting for antigen presentation [232]; (8) CT in combination with PTT, enhanced by vasculature remodeling [127]; (9) combination of PDT with chemodynamic therapy [130], and PDT with cuproptosis [131], (10) improving immune evading and tumor targeting properties of oncolytic virus [233]; (11) delivery of micellized GEM by

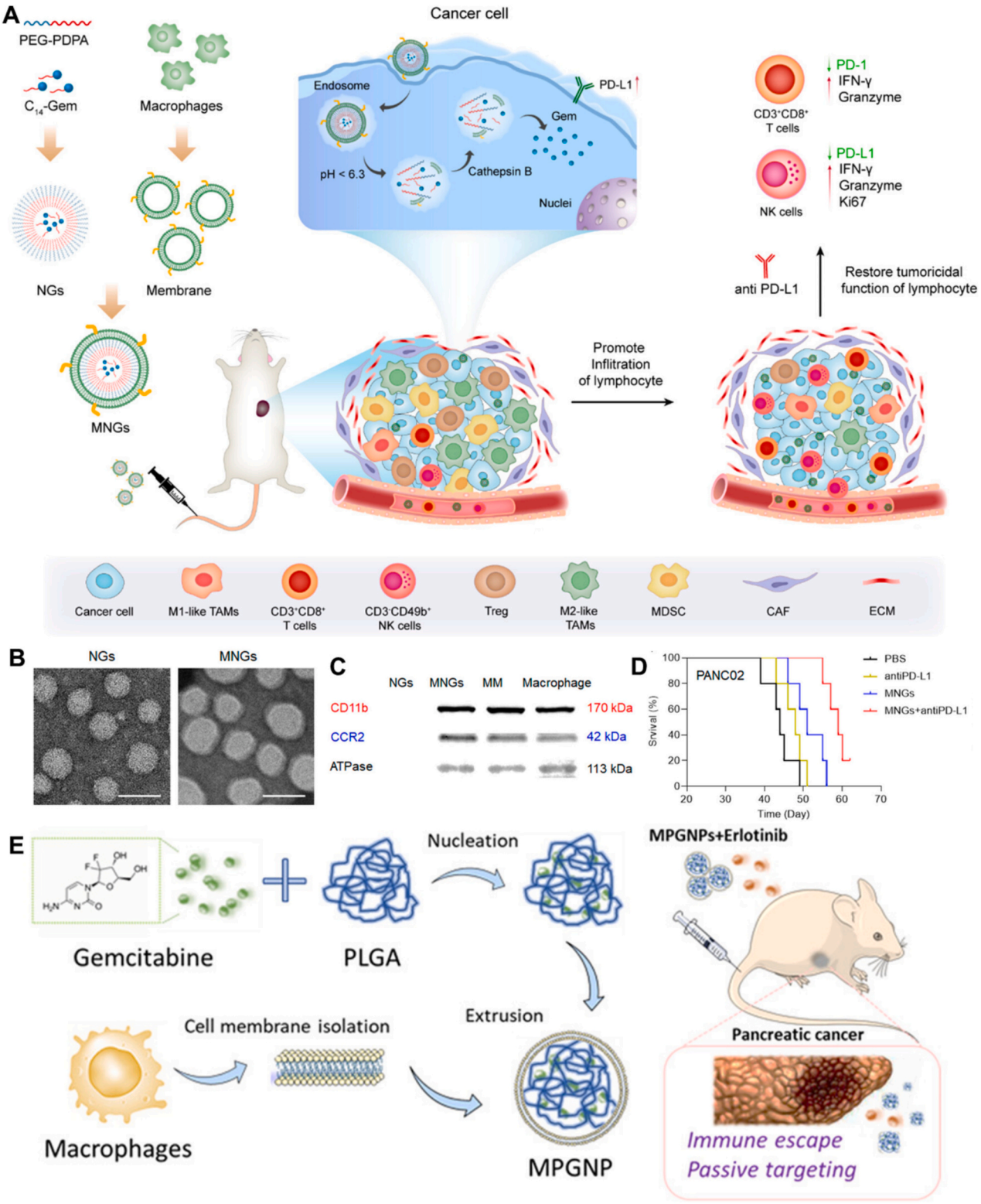

Fig. 12. (A) Schematic representation of the macrophage membrane-coated nano-GEM NPs (MNGs). MNGs were prepared by coating a macrophage membrane onto the nano-GEM NPs composed of pH-sensitive polymer PEG-PDPA and cathepsin B-responsive GEM prodrug C_{14}-GEM. MNGs promoted deep tumor permeation, and stimuli-responsive drug release towards strong immunomodulatory effects, such as eliminating the suppressive immune cells, and promoting the lymphocyte infiltration in tumors, amplifying anti-PD-L1 responses. (B) TEM images of NGs and MNGs; scale bar, 100 nm. (C) Expression of CD11b, CCR2, and ATPase in NGs, MNGs, MM, and macrophages by Western blot analysis. (D) Survival time and rate in PANC-2-Luc-induced PC models. Adapted with permission from [106]. Copyright American Chemical Society (2023). (E) Illustration of the MPGNP preparation including GEM loading and cell membrane isolation from macrophages. Reproduced with permission from [105]. Copyright American Chemical Society (2021). *Abbreviations:* PEG-PDPA, poly (ethylene glycol)-b-poly(2-(diisopropylamino) ethyl methacrylate); GEM, gemcitabine; NPs, nanoparticles; anti-PD-L1, anti-programmed death ligand 1; MNGs, macrophage membrane-coated nano-gemcitabine system, NG, nano gemcitabine system; MM, macrophage membranes; MPGNP, macrophage membrane-coated PLGA nanoparticle loaded with gemcitabine.

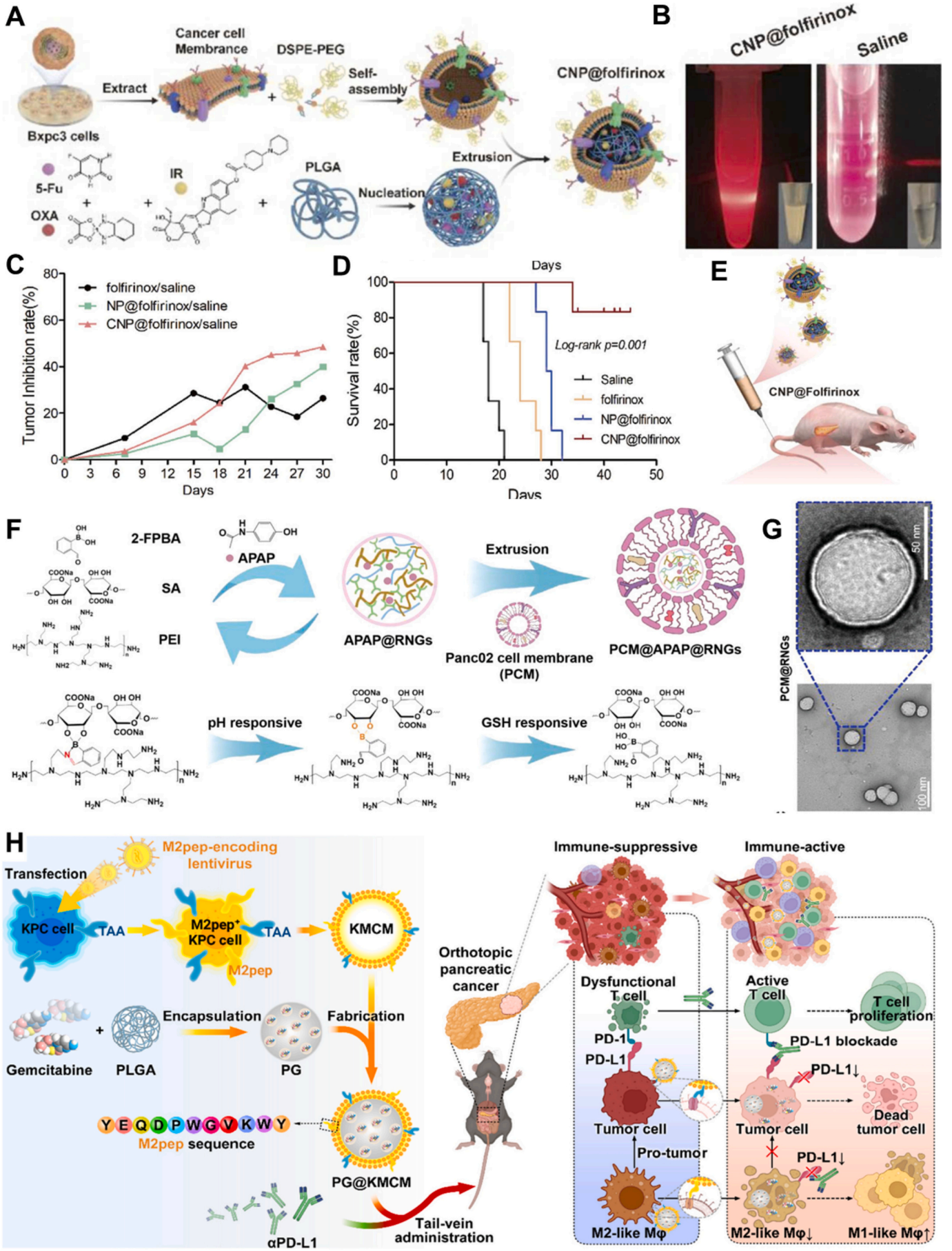

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Fig. 13. (A) Schematic illustration of CNP@FOLFIRINOX® system. (B) Visualization of dundar phenomenon of CNP@ FOLFIRINOX®. (C) Tumor growth inhibition. (D) Tumor survival assessment. (E) Administration of CNP@FOLFIRINOX; Adapted with permission from [129]. Copyright Elsevier (2023). (F) APAP@RNGs were prepared from 2-FPBA, SA, APAP, and PEI through inverse miniemulsion method. PCM@APAP@RNGs were obtained by a PCM coating onto APAP@RNGs surface. (G) TEM images of PCM@RNGs. Adapted with permission from [107]. Copyright John Wiley & Sons Inc. (2022). (H) Schematic illustration of dual-targeting biomimetic system for PC chemoimmunotherapy. Reproduced with permission from [125]. Copyright Springer Nature (2022). *Abbreviations:* RNGs, responsive nanogels; 2-FPBA, 2-formylbenzenebo-ronic acid; SA, sodium alginate; APAP, Acetaminophen; PEI, polyethylenimine; PCM, Panc-2 cell membranes.

means of a prodrug approach composed of vitamin E-GEM units encapsulated in biofunctional polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus®) micelles [234] and improved proteolysis-targeting chimeric (PROTAC) delivery [235].

3.3.4. Red blood cell membrane-coated nanosystems

Red blood cell (RBC) membranes can endow NP cores with improved immune evasion and circulation half-life properties. CD47 is a protein marker expressed at the surface of RBC membranes and a key player in immune escape properties [236]. Modulation of the TME of PC has also attracted increased interest, particularly in combination with other therapies. PC stroma normalization by decreasing its stiffness and promote ECM unpacking can improve blood perfusion and ameliorate drug accessibility to the tumor. Jiang et al. developed RBC membrane-coated gold nanorods for improved photothermal therapy of PC, in association with well-known hedgehog signaling inhibitor cyclopamine (Fig. 14. A) [108].

The RBC membrane coating conserved the biofunctional properties of the native RBCs namely improved circulation profile and reduced clearance by the immune system, without impacting photothermal activity of the gold nanorods. Cyclopamine-mediated ECM disruption together with pharmacokinetic improvements conferred by RBC membrane coating improved delivery of RBC membrane-coated gold nanorods delivery to PC and potentiated the photothermal effect (Fig. 14. B—F). Additionally, RBC membrane coating was applied to leverage blood circulation of PEG-PLGA NPs modified with stroma targeting FnBPA5 peptide and loaded with doxorubicin and retinoic acid [123]. Retinoic acid was employed for exerting stroma remodeling effect mainly by modulating the function of Golgi Apparatus Complex in CAFs and facilitate doxorubicin delivery to PC. Additional studies have explored ICG-mediated PTT in *in vivo* PC models using RBC membrane-coated MOFs [222] as well as cyclopamine stroma remodeling effect by RBC membrane-coated PLGA NPs, in combination with enhanced PTX delivery recurring to RBC membrane-coated NPs [223].

3.3.5. Stem cell membrane-coated nanosystems

Stem cell membrane coated NPs evidence enhanced biocompatibility, prolonged blood circulation half-life, and ability to target inflamed/diseased tissues, and pose as efficient delivery systems for PC-targeted therapies [87]. As an example, mesenchymal stem cell membrane-coated PLGA NPs were loaded with doxorubicin and showed interesting targeting abilities in PC tumor models, including patient-derived PC cells [109]. The stem cell membrane showed expression of C—C chemokine receptor (CCR) type 1 (CCR1), CCR2, and CXCR4 which were suggested to mediate migration towards PC cells and the tumor homing effect. PC patients derived cells were positive to surface markers such as CD133, CD44, EpCAM and CD24.

3.3.6. Cancer-associated fibroblast membrane-coated nanosystems

CAF cell membrane-coated nanosystems were recently developed to tackle PC. The first study comprised regulation of metabolism of nicotinamide, vitamin B3, nicotinamide adenine dinucleotide (NAD+), in pancreatic CAFs, by encapsulation of a siRNA targeting nicotinamide *N*-methyltransferase (NNMT) – which decreases vitamin B3 levels by methylation - in MSNs further coated with a CAF membrane for improved stroma targeting (Fig. 15. A, B) [112].

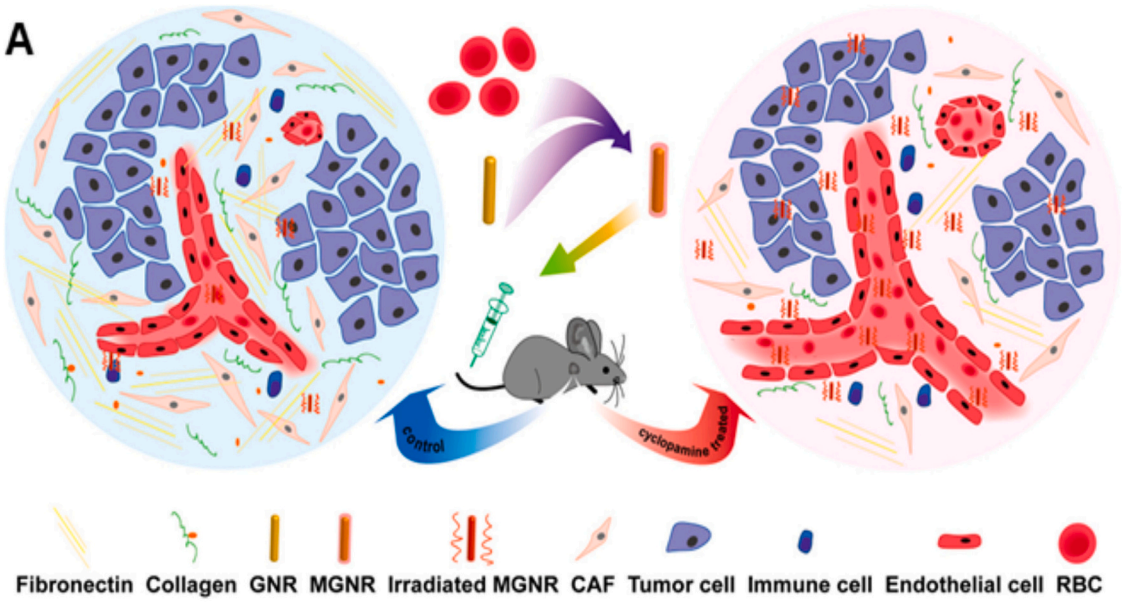
The CAF membrane-coated system was further combined with PANC-2 cell membrane-camouflaged GEM MSNs and incorporated in a hydrogel for disrupting vitamin B3 metabolism and enhanced PC chemotherapy, by means of synergistic epigenetic and chemotherapeutic concerted mechanism. Inhibition of CAF-overexpressed NNMT was able to reprogram altered immunosuppressing vitamin B3 metabolism in CAFs and restore the pool of epigenetic modulators S-adenosyl methionine (SAM) and nicotinamide adenine dinucleotide (NAD+). Hence, metabolic circuit of vitamin B3 was rewired through epigenetic modulation of CAFs by reprogrammed histone methylation and deacetylation leading to CAF normalization and diminished CAF-mediated release of immunosuppressive and chemoresistance-inducing signals and resulted in decreased levels of tumor-resident CSC pool overly associated with emergence of multidrug resistance phenotypes, together with immunosuppressing MDSCs and regulatory T cells, while increasing infiltration of cytotoxic T cells. The two-in-one system demonstrated efficient PC eradication through an elegantly designed epi-immunochemotherapeutic mechanism and elicited long-term T cell memory.

A second work reports on CAF-coated liposomes loaded with BET inhibitor JQ1 and CAF-remodeling pirfenidone for reducing stroma fibrosis, metabolic reprogramming and enhanced JQ1 delivery for anticancer effect (Fig. 15. C) [224]. CAF membrane coating together with TAT peptide functionalization were leveraged as a strategy for efficient PC targeting and deep tumor penetration. Results showed inhibition of CAF-mediated ECM secretion and tumor glycolytic pathway by pirfenidone, which is often stimulated as immediate source of energy for cancer cells, as well as modulation of TME towards less hypoxic nature and improve sensitization of PC cells to JQ1 for inducement of PC apoptosis. Other recent study reported the combination of stroma remodeling losartan with carbon monoxide-producing iron carbonyl (FeCO) encapsulated in polydopamine NPs coated with CAF cell membranes, which were functionalized with PC-targeting peptide, achieving double CAF and PC targeting, stroma remodeling and enhanced PC inhibition [225].

3.3.7. Hybrid cell membrane-coated nanosystems

The ability to combine two or more cell membranes from distinct sources further extends the functionality and versatility of cell membrane-coated nanosystems by merging attributes of each membrane thereby enriching overall performance of cell membrane coated nanosystems [237–239]. For that, different hybrid cell membranes have been assembled, and the most common ones combine RBC membranes with cancer cell membranes (CCMs) with the intent to fuse the immune evading and prolonged blood circulation properties of RBC membranes with the homotypic targeting and antigen-presenting ones of CCMs, assembling RBC-CCM hybrid membrane-coated systems [240–243]. Another commonly employed membrane pairs to coat NP cores include macrophage cell membrane-CCM [244,245], platelet cell membrane-macrophage cell membrane [246], platelet cell membrane-RBC membrane [247], platelet cell membrane-CCM [248], to list a few.

Regarding PC-targeted strategies, both hybrid macrophage cell membrane-CCM [132] and red blood cell-CCM [133] have been explored as of now. In the first case, GEM and erlotinib were co-loaded with siRNA for stroma normalization and synergistic anticancer action of GEM and erlotinib. GEM was loaded by chemical conjugation to polycation PEI through disulfide bond (−ss-), which was then coupled to β-cyclodextrin (β-CD); the latter employed for loading erlotinib (ERL) in the hydrophobic cavity. PEI enabled direct complexation with IRAK4 siRNA (siIRAK4) through electrostatic interactions, assembling a final



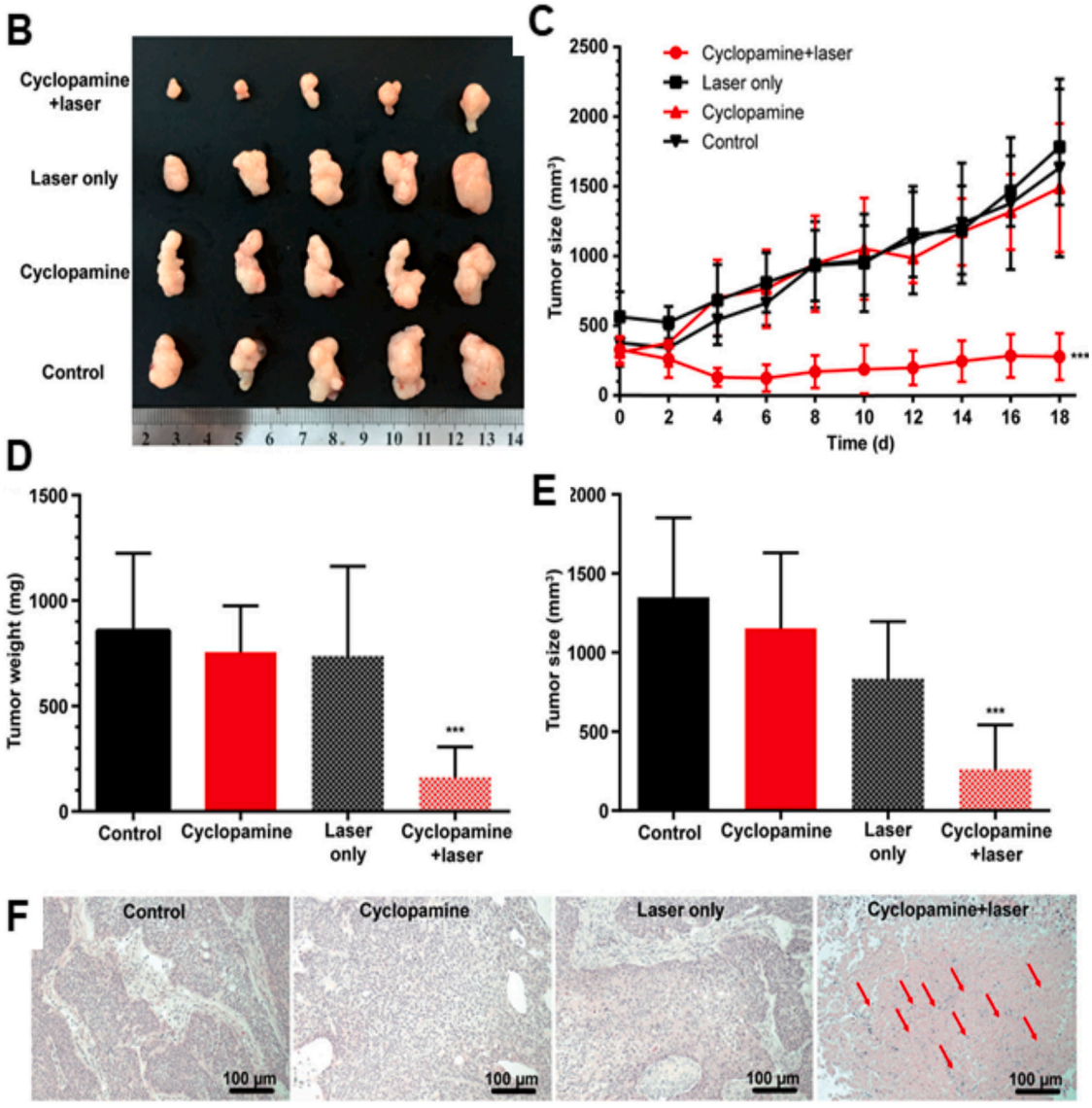


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Fig. 14. (A) Schematic illustration of MGNRs. After treatment with stroma remodeling agent cyclopamine, ECM components were disrupted, and tumor vessels were decompressed and normalized, resulting in enhanced blood perfusion and enhanced delivery of MGNRs (B—F). PTT efficacy. (B) Tumor xenograft photos obtained at the study end point. (C) Tumor size evaluation during the experiment. (D) Tumor weight and (E) tumor size evaluation at the study end point. (F) Staining of tumor slices from different treatment groups. Red arrows represent tumor necrosis. Adapted with permission from [108]. Copyright Royal Society of Chemistry (2017). *Abbreviations:* MGNRs, membrane-coated gold nanorods; ECM, extracellular matrix; PTT, photothermal therapy.

nanostructured core GEM-ss-PEI@siIRAK4-β-CD@ERL coated with hybrid cancer-macrophage cell membrane (siIRAK4/Er@GEM-SS-PC-M, in which PC represents PEI-*β*-CD, and M the hybrid cell membrane coating) (Fig. 16. A, B) [132]. Interestingly, the coating changed the surface charge of the system to −16 mV and showed presence of macrophage surface markers CD45 and CD14 mediating the immune escape properties, as well as CD135, and cell adhesion marker E-cadherin was detected on the CCM and mediated homotypic targeting of PC. The results demonstrated that IRAK4 blockade significantly reduced desmoplastic stroma, enabling deep tissue penetration and display enhanced anticancer activity, extended survival and metastasis inhibition in PC mice models, including patient-derived tumor xenografts.

PC displays a dense desmoplastic stroma barrier which broadly undermines drug delivery due to the difficulty of NPs to transverse stroma and reach tumor site, limiting tumor biodistribution. In other to counteract this issue, doxorubicin and ECM degrading enzyme hyaluronidase were loaded with high efficiency in cationic MSNs functionalized with an intermediate pH-responsive lipid bilayer which was further coated with hybrid RBC-cancer cell membrane fused with pH-responsive liposome for acid-responsive drug release (Fig. 16. C-E) [133]. The cationic properties of the system and the large pore size of MSNs improved loading capability of hyaluronidase. The hybrid cell membrane coated system showed multifunctional properties and enhanced anticancer activity in *in vivo* PC model, namely by facilitation stroma penetration by hyaluronidase-mediated stroma remodeling, enhanced blood circulation half-life imparted by RBC membrane functionalization and improved tumor targeting enabled by the homotypic BxPC-3 PC cell membrane.

Cell membrane-coated NPs can also be leveraged to improve stability and drug retention through fine-tuned electrostatic interaction and membrane rigidity modulation while preserving relevant targeting and immune escape surface receptors [249]. The electrostatic stabilization, membrane affinity and rigidity attained with the negatively charged hybrid membrane composed of red blood cell-PC hybrid cell membrane coating the positively charged ROS-responsive polymer NP system composed of a photosensitizer and ROS-sensitive Pluronic® F127, efficiently improved nanoparticle stability, prevented drug leakage during circulation, enhanced PC membrane-mediated targeting, and enabled site-specific drug release upon light activation [249].

In brief, fabrication of hybrid cell membrane-coated nanosystems represents an attractive strategy to improve functionality of PC-targeted systems by combination of cell membrane portions extracted from distinct cell sources and contribute to overall enhanced tumor biodistribution and accumulation. Taking into consideration all cell types can be explored to coat NP cores, the versatility and tunable properties of single and hybrid cell membrane-coated nanosystems show great promise in the near future for preparing advanced PC-directed therapies.

3.4. Cell membrane nanovesicles

Cell membrane nanovesicles, also known as cell ghosts, nanoghosts, hybrid exosomes or exosome mimetics, constitute nano-sized biomimetic cell membrane-derived vesicles which reproduce main surface repertoire molecules expressed on native cell membranes and display similar structure to exosomes while improving manufacturing and loading processes [238,250]. The manufacture process of cell membrane nanovesicles generally involve extrusion of cell membrane pellet through polycarbonate membrane to form the spherical nanosized cell membrane-like structures. When compared to EV production, the yield is considerably higher, while biocompatibility and targeting features are maintained [251]. In this section, engineered exosomes with lipid bilayers are also considered cell membrane nanovesicles due to their posterior modification/fusion with liposomes.

When compared to liposomes, cell membrane nanovesicles maintain lipid bilayer structure and an aqueous core but are naturally enriched with a biomimetic stealth conferred by vast array of proteins and glycoproteins that orchestrate intercellular communication processes. Hence, cell membrane nanovesicles constitute a biomimetic alternative to traditional liposomes regarding enhanced biocompatibility, functionality and targeting. Several studies have reported thus far the preparation of cell membrane nanovesicles produced from source cells including mesenchymal stem cells [252], cancer cells [253], immune cells such as neutrophils [254] and dendritic cells [255]. Some PC-targeted cell membrane nanovesicles have been explored till this day, discussed further (Table 8).

3.4.1. Single cell membrane nanovesicles

Co-administration of CT drugs with different target mechanisms can synergistically improve cancer therapy by simultaneous affecting different pathways mediating cancer cell survival and proliferation, at the same time minimizing multidrug resistance development by cancer cells. Besides improving serum stability and safety of drug combinations, co-delivery *via* drug delivery systems may enable spatiotemporal release and biodistribution in cancer tissues. Cell membrane nanovesicles can also be engineered to act as artificial nano-based antigen-presenting cells, nanovaccines and facilitate maturation of antigen-presenting cells thus eliciting strong immune responses in combination with IT [258].

GEM plus Nab-PTX association has shown encouraging results for treating PC patients in the clinical setting when compared to GEM monotherapy. Comparetti et al. co-encapsulated nucleoside analogue GEM and microtubule-stabilizing PTX in PC cell membrane nanovesicles for synergistic PC-targeted delivery [113]. Surface antigens and adhesion molecules displayed on cell membrane nanovesicles surface could improve the specificity of the nanosystem to PC cells and enhanced anticancer activity by maximizing interaction PC cell surface receptors, as opposed to synthetic liposomes counterparts. The influence of the nanosystem on immune cells from donors was assessed by analyzing expression of surface markers required for antigen presentation in monocytes and DCs from healthy donors. The nanovesicles were able to induce immune cell activation and activate antigen-presenting pathway traduced by increased expression of HLA—DR protein, which serves as MHCII cell surface receptor typically found on APCs, and co-stimulatory markers, namely CD80, CD83, CD86 and PD-L1, in both tested cells and in a greater extent when compared to free GEM and PTX association [113]. Further studies on mixed lymphocyte reaction assay showed, contrarily to CT-loaded nanovesicles, the membrane protein content of the nanovesicles alone was able to induce significant proliferation of T cells, which may suggest DC capture, processing and surface presentation of nanovesicles-anchored PC cell surface proteins to T cells. This strategy may potentially function simultaneously as CT-assisted PC cells killing and as nanovaccine to re-educate APCs and effector T cells towards nano-enabled PC ITs.

Another strategy consisted in fabricating Mia-PaCa-2 cell membrane nanovesicles loaded with PTX and M2 macrophage cell membrane nanovesicles loaded with pexidartinib, which is a CSF-1R inhibitor to improve stroma permeation and anticancer activity of PTX [259].

3.4.2. Hybrid cell membrane-liposome nanovesicles

Combination of synthetic lipid bilayers (*e.g.* liposomes) with cell

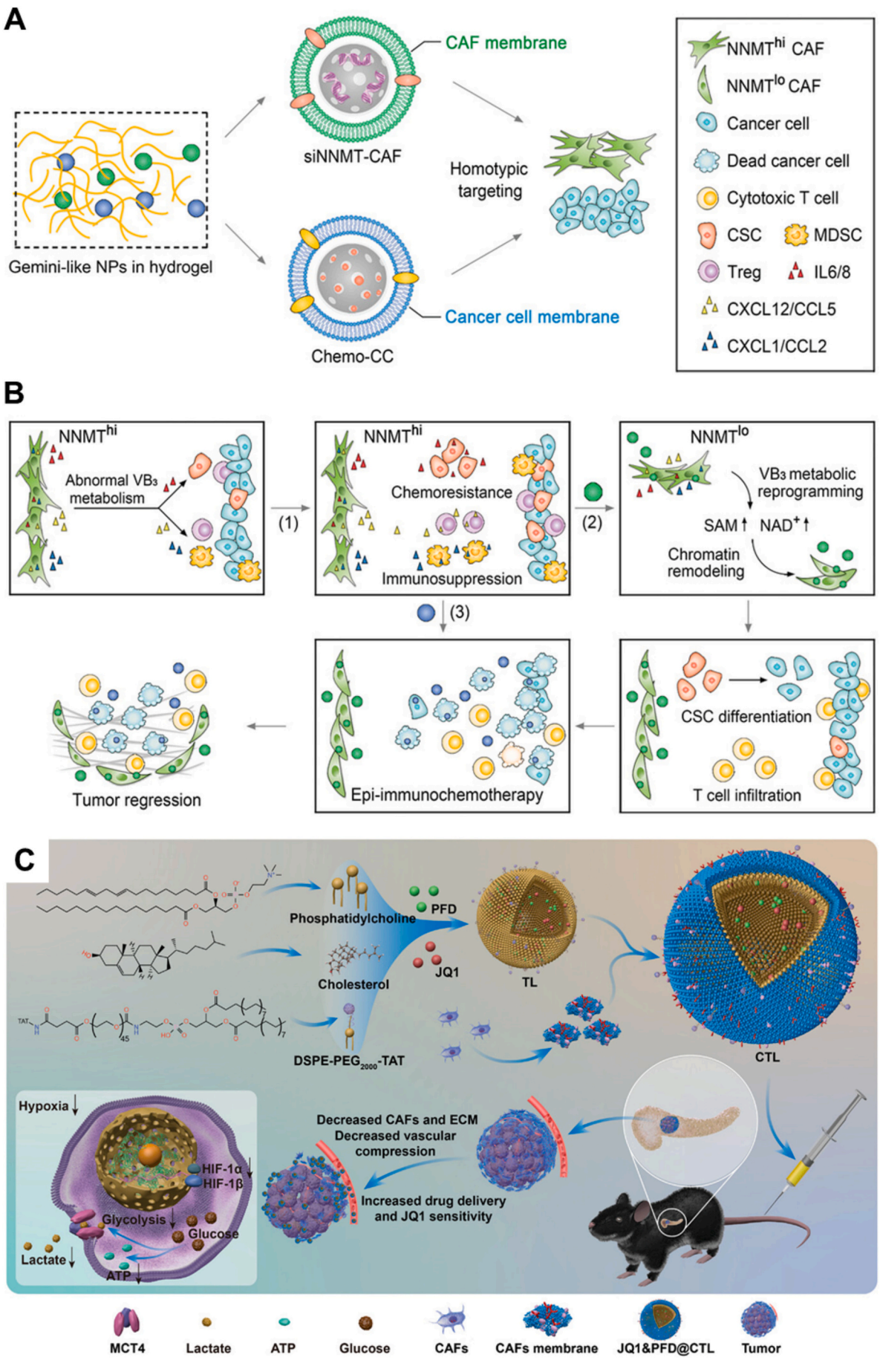

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Fig. 15. (A) Schematic illustration of the hydrogel platform incorporating CAF- and cancer cell-targeted NPs. (B) Schematic illustration of synergistic actions of Gemini-like NPs against chemoresistant cancer: 1) the altered VB_3 metabolism in CAFs promotes CSC expansion and immunosuppressive cell recruitment, leading to chemoresistance and immune evasion; 2) siNNMT-CAF reprogram VB_3 metabolism to restore SAM and NAD^+ reservoirs and transform CAFs into quiescent fibroblasts *via* chromatin remodeling, inducing CSC differentiation and cytotoxic T cell infiltration; 3) Chemo-CC (chemotherapy) coordinate with siNNMT-CAF-mediated chemosensitivity recovery (epigenetic therapy) and immune activation (immunotherapy) for regression of chemoresistant tumors. Reproduced with permission from [112]. Copyright John Wiley & Sons Inc. (2023). (C) The synthesis of JQ1&PFD@CTL, along with its role in inhibiting CAFs and the formation of the stromal barrier, enhancing drug delivery, improving the hypoxic tumor environment, inhibiting tumor glycolysis, and simultaneously increasing the sensitivity of JQ1. Reproduced with permission from [224]. Copyright John Wiley & Sons Inc. (2023). *Abbreviations:* VB_3, vitamin B3; CAF, cancer-associated fibroblasts; CSC, cancer stem cell; SAM, S-adenosyl methionine NAD+, nicotinamide adenine dinucleotide.

membrane nanovesicles have also received increased attention [238]. For example, dendritic cell membranes were extracted and fused together with synthetic lipid bilayers composed of PEGylated lipids encapsulating celastrol, through sonication and extrusion process and assembling hybrid liposome-cell membrane nanovesicles against KRAS-mutant PC cells (Fig. 17. A-D) [114]. This strategy could expand the reactive sites of cell membrane nanovesicles and afford easily tunable hybrid biomimetic structures capable of recapitulating surface composition of DC-derived exosomes such as several integrins, annexins and CD47 adhesion-related protein MFGE8, tetraspanins (CD81, CD9) and ICAM-1. Other surface-exposed molecules include membrane trafficking-related molecules, namely, Ras-related protein Rap-1b (RAP 1B), RHO protein GDP dissociation inhibitor (Rho GDIs) and annexins (Fig. 17. D—F). This strategy could enhance the targeted delivery and accumulation of celastrol at tumor sites and improve anticancer activity of the nanosystem (Fig. 17. G-I).

Platelets constitutively express P-selectin molecules on their cell membranes, which can bind to overexpressed CD44 receptors on wide variety of cancer cells [210]. Based on this interaction, Geng et al. explored a platelet cell membrane-based nanoprobes acquiring biofunctionalities conferred by platelet cell membranes such as antiphagocytic, prolonged blood circulation half-life, tropism to inflamed tissues and intrinsic cancer cell targeting [115]. First, the platelet cell membrane (-28.1 ± 1.2 mV) was extracted from mice blood, membrane proteins extracted and fused with IR 1048-loaded liposomes (149.4 ± 3 nm; -16.3 ± 0.7 by extrusion assembling hybrid biomimetic proteolipid liposome (119.8 ± 2 nm; -22 ± 1.8 mV) enriched with platelet cell membrane surface proteins. The hybrid biomimetic liposomes loaded with IR 1048 were aimed at *in vivo* NIR-II-mediated imaging of several cancers including PC [115]. Decreased uptake (2.82-fold) by macrophages of the hybrid biomimetic liposomes probably due to surface-exposed "don't eat me" signal CD47. Interestingly, *in vivo* studies in subcutaneous xenograft SW1990 PC mice models (injection of NPs 0.3 mg/kg IR 1048 dose) showed a more uniform tumor distribution of photoacoustic signal for IR 1048-loaded biomimetic liposomes when compared to IR 1048-loaded liposomes, attesting their enhanced targeting and photoacoustic imaging properties for PC imaging. In another experiment, DOX and ICG were successfully loaded in liposome-PC cell membrane nanovesicles which showed enhanced anticancer performance by combining strong PTT and PDT effect of ICG with cytotoxicity-inducing DOX, eliciting the potential of the cell membrane coating technology to allow deep tumor penetration and amplified phototherapy responses [256].

3.4.3. Hybrid cell membrane nanovesicles

Cell membrane-based nanovesicles can be tailored to accommodate cell membrane material from two or more distinct cell sources by extrusion, which improves functionality while maintaining stability, drug loading and immunological profile. Besides cell membrane, intracellular organelles and secreted vesicles (such as EVs and OMVs) can be used for further hybridization with membrane derived nanovesicles and enriching surface repertoire and targeting abilities of the biomimetic nanosystem. In a recent work, PC cell membrane-OMV nanovesicles were prepared for combined PTT and IT based on ICG loading in the hydrophobic lipid bilayer compartment and benefiting from immunostimulant properties of OMV surface proteins [257]. The potential of cell membrane-based nanovesicles is significant, as combination of cell membrane materials from distinct cell sources allows for selective enrichment of features related to the inherited surface repertoire and contributes to versatility of the nanosystem.

3.5. Blood protein-based carriers

Human serum albumin (HSA) is the most abundant protein in human plasma with a molecular weight of 65–70 kDa and circulation half-life of 20 days, approximatedly [260]. Albumin nanoparticles have been extensively explored as suitable nanosystems for targeted drug delivery to tumors, based on their enhanced biocompatiblity, biodegradability, prolonged blood circulation and tumor accumulation potential, culminating in 2005 approval of HSA-bound PTX (Abraxane®, Nab™-PTX), broadly used in PC tehrapy in combination with GEM. While some studies have also explored bovine serum albumin (BSA) as carrier for therapeutic drug delivery, HSA is often preferred due to decreased immunogenicity and higher suitability for human-based applications and scale-up [260,261]. In addition to the clinical success of Nab-PTX, the manufacture of novel albumin-bound chemotherapy drug formulations has received increased interest, also in the context of PC. The most significant example is GEM, in which encapsulation in albumin NPs has provided interesting anticancer effects in mice models of diesase, either by building a GEM-fatty acid prodrug (4-N-myristoyl-gemcitabine (GEM—C14)) [117,262], size ~150 nm, and exerted the best anticancer effects and safety in BxPC3 tumor bearing mice models. The NPs were prepared through Nab™ technology in order to control better the size, distribution profile and stability of the NPs, potentially favouring blood circulation, EPR-mediated tumor accumulation and size-related uptake by immune cells [117].

Other studies include GEM conjugation to BSA through a highly stable amide bond, followed by high pressure homogenization, obtaining GEM-loaded BSA NPs size ~150 nm, undergoing internalization through clathrin-mediated endocytosis [118]. This strategy allows for increased GEM physicochemical and metabolic/enzymatic stability and improved retention inside BSA NPs structure. Other conjugation strategies employed in the context of PC include linking GEM to HAS by means of a cathepsin B-responsive linker, assembling GEM-HAS conjugates with the ability to further accommodate dye IR780 [263]. BSA NPs were also loaded with plant-derived compounds, such as α-solanine [264] and parvifloron D [116]. In a recent study, PvD-loaded BSA NPs were also explored as *in vitro* EGFR-targeted nanosystems through surface functionalization with EGFR-targeted molecules erlotinib and cetuximab, due to common overexpression of EGFR in PC cell lines [116]. Other targeting ligands explored were arginine-glycine-aspartic acid (RGD) peptide, targeting integrin αvβ3 receptor at the surface of PC cells, for bolstered cellular uptake of GEM through a receptor-mediated endocytosis mechanism [265].

Albumin NPs can also be modified with cationic groups or polymers to explore nucleic acid delivery to PC. In one study, BSA-PDMAEMA conjugate in which cationic nature of PDMAEMA allowed condensation of antisense oligonucleotide ISIS5132, was developed in the form of a BSA corona with a PDMAEMA/oligonucleotide core (size <100 nm) with significant tumor growth inhibitory effects exerted in a AsPC-1-bearing mice [266]. ISIS5132 is able to inhibit c-raf-1, a key player in mitogen-activated protein (MAP) kinase pathway involved in tumor

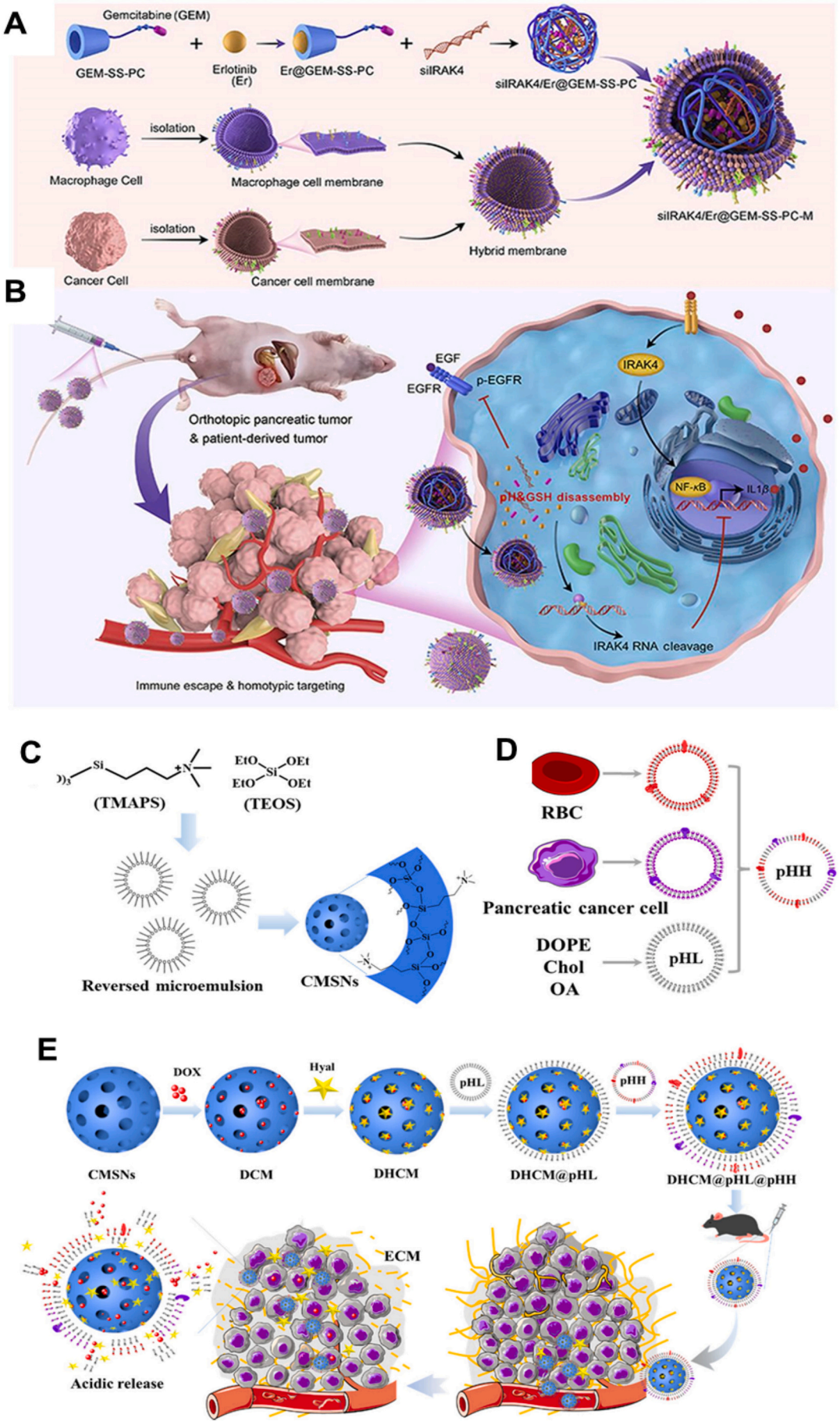

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Fig. 16. (A) Schematic illustration of siIRAK4/Er@GEM-ss-PC-M. GEM was conjugated to PC by a GSH-responsive linker to form a GEM prodrug, followed by encapsulating the Erlotinib (Er) *via* host–guest molecular interaction and loading with the IRAK4 siRNA to assemble cell membrane-coated NPs (siIRAK4/Er@GEM-ss-PC-M). (B) Schematic illustration of targeted delivery of multidrug-loaded siIRAK4/Er@GEM-ss-PC-M. Reproduced with permission from [132]. Copyright Elsevier (2022). (C) Synthesis of the CMSNs through a reversed microemulsion reaction, (D) preparation of the pHH, and (E) fabrication of the DHCM@pHL@pHH NPs for PC-targeted delivery and deep tumor penetration *in vivo*. Reproduced with permission from [133]. Copyright American Chemical Society (2023). *Abbreviations:* siIRAK4, IRAK4 siRNA; Er, erlotinib; GEM, gemcitabine; PC, β-cyclodextrin (β-CD)- polyethylenimine; M, hybrid membrane; GSH, glutathione; NPs, nanoparticles; CMSNs, cationic mesoporous silica nanoparticles; pHH, pH-sensitive hybrid cell membrane; pHL, pH-sensitive liposome; DHCM, hybrid cell membrane/liposome-coated drug-loaded nanosystem.

growth and progression.

The unique PC microenvironment can be characterized in part by the specific genetic makeup of PC cells and metabolic alterations driving PC progression and metastization, which can be collectively explored to enhance drug delivery to PC. A recent study explored the influence of KRAS mutation and neonatal Fc receptor (FcRn) expression in PC on delivery of DOX/albumin NPs to PC and improve sensitization of PC by a concerted mechanism tackling albumin catabolism [267]. Firstly, KRAS-mutated PC often displays both enhanced macropinocytosis and enhanced catabolism of extracellular proteins, such as albumin, as nutrient source. Secondly, FcRn expression in PC cells could act as an albumin catabolism regulator, and its down-regulation in KRAS-mutated PC could drive albumin intracellular trafficking towards decreased albumin recycling and enhanced degradation. Interestingly, *in vivo* results in MIA-PaCa-2-bearing mice models showed KRAS-mediated enhanced macropinocytosis increased doxorubicin-albumin NPs uptake and degradation, as well as very low FcRn expression levels hindered albumin recycling pathway, collectively improving sensitization of PC to doxorubicin/albumin NPs, which was not verified in the free doxorubicin group. The enhanced drug delivery effect of drug-loaded albumin NPs can also benefit from common albumin receptors glycoprotein 60 (GP 60) and secreted protein acidic and rich in cysteine (SPARC), by means of enhanced targeting mechanism. GP60 is mainly expressed in endothelial cells associated with vasculature, while SPARC is often overexpressed at cancer cell membranes [268]. Based on this, a metabolic nanoregulator aimed at tTME-enriched SPARC was developed by encapsulating plant-derived compound citrus flavonoid narigenin and biganides, towards concerted glutaminolysis and glycolysis inhibition, respectively (Fig. 18. A) [269].

Besides the augmented macropinocytosis observed in KRAS-mutant PC and facility towards albumin NP internalization, the dysregulated metabolic pathways that privilege extensive glucose production through glycolysis and glutamate by glutaminolysis, non-cancerous cells typically recur to oxidative phosphorylation for energy production, and the nanoregulator can preferentially impact PC cells (Fig. 18. A). *In vivo* results in orthotopic KPC1199 mice models showed enhanced accumulation in PC TME, probably related to the SPARC overexpression, and significant micropinocytosis-dependent uptake of the nanoregulators and successfully inhibited glycolysis and glutamate production. The influence of the nanoregulator on the highly fibrotic and highly immunosuppressed TME was further assessed (Fig. 18. B) and demonstrated efficient CAF reprogramming by decreased expression of fibronectin, α-smooth muscle actin (α-SMA), collagen and fibroblast activation protein (FPA) (Fig. 18. C—F). The additional polarization of pro-tumoral immunosuppressive M2 macrophage subtype towards anti-tumoral M1 macrophage suggested the nanoregulators could reactivate the immunosuppressed TME. Additional results demonstrated the suitability of the nanoregulators towards elevated autophagy, reduction of tumor growth and metastasis and prolonged survival rate of the PC mice models when compared to controls. Another exciting strategy was developed to normalize PC stroma and enhance GEM delivery to PC cells, in which an albumin-conjugated flumethasone delivery system could successfully deactivate PSCs towards more quiescent state, decrease ECM production and induce stroma normalization majorly benefiting GEM delivery and anticancer action on *in vivo* PC models [270].

Ferritin is another bioprotein naturally present in human plasma, playing a key role in iron storage and delivery functions and presents a 24-subunit structure arranged in hollow nanometer-sized spherical shape (~12 nm) with an inner cavity [271]. Ferritin NPs have been explored as interesting drug delivery nanosystems based on their biocompatibility, natural origin, and ability to accommodate and protect drug molecules at their hollow core. The nutrient supply of cancer cells includes elevated iron intake, which drives overexpression of transferrin receptor 1 (TfR1, CD71) in cancer cells. Hence, the interaction of ferritin with transferrin receptor 1 (TfR1, CD71) enables maximized uptake by TfR1-overexpressing cancer cells, acting as a targeting ligand mediating active targeting of cancer cells.

In one study, the role of carbachol-mediated neurostimulation and atropine-mediated neuroinhibition of PC TME was studied [119]. The drug-loaded ferritin nanocages had size ~ 13 nm, and negative surface charge (~ −7 mV) and were able to retain the drugs in circulation and achieve tumor accumulation. Interestingly, ferritin/atropine NPs blocked cancer cell-nerve crosstalk and suppressed neurogenesis in PANC-1-luc PC models, as opposed to tumor promoting effects of ferritin/carbachol NPs. Atropine acts as an antagonist of muscarinic receptors on cancer cells and negatively interfered with cancer cell-nerve crosstalk, possibly by (1) blockage of muscarinic receptors on PC cells, which (2) decreases activity of tumor growth-promoting downstream signal transduction pathways such as PI3K/AKT/mTOR, leading to (3) PC growth inhibition and decreased production of neurotrophic factors and (4) limiting neoneurogenesis in the PC microenvironment and tumor-innervating nerve cells. Neuroinhibition in PC microenvironment (5) decreases production of specific tumor-promoting neurotransmitters like acetylcholine thus (6) limiting tumor proliferation and survival. This strategy illustrates the capability of biomimetic nanosystems to enhance safety and therapeutic profile of PC modulating drugs with ability to halt PC progression by inhibiting protumorigenic cancer-nerve crosstalk. In another experiment, the structure of ferritin was genetically modified to improve selectivity towards cancer cells, by coupling masking polypeptides including a MMP-responsive peptide linker and carrying Genz-644,282, a non-CPT topoisomerase I inhibitor [120]. The masking effect could protect unwanted interaction of the ferritin NPs towards healthy cells and prolong blood circulation half-life on account of high solubility conferred by the masking polypeptides, thus potentiating EPR effect. Besides surface modification of the ferritin NPs, drug binding was also increased by fine-tuning amino acid residues located at the hollow core, as drug loading mostly occurs on electrostatic interactions established between drugs and inner amino acid residues [120]. Results showed significant therapeutic effect in HPAF II cell, and PaCa44 bearing PC mice models and exhibited superior performance when compared to the clinically-approved Nab™-PTX [272].

4. Challenges and future prospects

Biomimetic nanosystems are receiving increasing attention regarding their expanded targeting features and biointerfacing [273]. Particularly, cell membrane-coated nanosystems can prolong blood circulation of nanoparticle cores, avoid immune clearance [274] and provide selective targeting features in *in vivo* models of disease, including in PC. Cancer cell membrane-coated nanoparticle cores display additional tumor targeting attributes by a homotypic mechanism and expose relevant surface markers to engage in immunomodulation

Table 8
Examples of cell membrane nanovesicles explored for PC therapy.

Membrane	Drug	Size (nm)	ZP (mV)	Dosage	Model	Results	Ref
PC cell membrane							
PC cell membrane nanovesicles (PANC-1 cell membrane)	GEM + PTX	152	−4	–	Panc-1 cells HEPA-RG cells	- ↑ interaction with PC cells *vs* hepatic cells - ↑ expression of HLA-DR, CD80, CD83, CD86, and PD-L1 in APCs - ↑ contact of T cells with PC cell surface	[113]
Hybrid PC cell membrane-liposome nanovesicles	ICG + DOX	106	−18	i.v. DOX 2.5 mg/kg + 0.5 mg/kg ICG 808 nm laser (1 W/cm^2, 5 min, 24 h after), every 2 days for 8 days	Subcutaneous SW1990 tumor-bearing nude mice	- ↑ tumor targeting - ↑ tumor penetration - ↑ NIR-II fluorescence imaging intensity. - ↑ anticancer activity by combining DOX with ICG-mediated PTT and PDT	[256]
Dendritic cell membrane							
Hybrid DC membrane EV-PEGylated liposome nanovesicles	CLT	150	−15	i.v., CLT dose of 2 mg/kg, every 5 days for 4 times	PANC-1 tumor-bearing nude mice	- ↑cellular uptake when compared to sole liposomes - ↑CLT tumor biodistribution and pharmacokinetics - ↓tumor volume - ↑apoptotic performance of CLT	[114]
Platelet cell membrane							
Hybrid platelet membrane-liposome nanovesicles	IR 1048	120	−22	i.v., formulation with IR 1048 dose of 0.3 mg/kg	Subcutaneous SW1990 tumor-bearing nude mice	- ↑ *In vivo* photoacoustic imaging (wavelength of 1064 nm, 12 h after injection adjusted to 10 mJ/cm) - CD44-P-selectin-mediated cellular uptake - ↓ uptake by phagocytes (3-fold) when compared to liposomes	[115]
OMV membrane							
Hybrid OMV membrane-PC cell membrane nanovesicles	ICG	53	−13	i.v. 1 mg/kg, 100 μL + 808 nm, 1.5 W/cm^2 laser irradiation (3 min)	PANC-2 tumor-bearing nude mice	- Combination of phototherapy with immunotherapy - ↑ tumor accumulation - ↓ uptake by immune cells - ↑ PTT performance *vs* free ICG - ↑ CD3+ T cells and ↓immunosuppressive CD206+ cells - suggested OMV-mediated immune stimulating properties	[257]

Abbreviations: PC, pancreatic cancer; GEM, gemcitabine; PTX, paclitaxel; PD-L1, programmed death ligand 1; APCs, antigen-presenting cells; DC, dendritic cell; CLT, celastrol; i.v., intravenous administration.

strategies. The versatility of cell membrane surface bioengineered NPs as PC targeted delivery systems of therapeutic agents may provide a novel strategy for establishing next-generation multicomponent and multifunctional PC therapies.

Several nanosystems have been subject of clinical trials and, as of the date of this review, are at various stages of development; a few have been approved for PC therapies (Table 9). For instance, Abraxane®, already approved for other cancer types in 2005, was approved in 2013 for PC therapy, used in combination with GEM. Other clinical trials involving Abraxane® in PC therapy involve other drug combinations and are not shown here as the authors pretend to focus on each nanosystem instead of the available combinations in the clinic. Other nanosystems approved for PC therapy are Onivyde® which is PEGylated liposome IRT, and is being tested in different combinations with chemotherapy drugs. Micellar PTX (Genexol®) was approved in Japan for PC treatment and comprehends the first micelle-based product approved for cancer therapy. Other nanosystems approved for other cancer types have been subject of exploration in PC, particularly in combination with other drugs. Additional nanosystems that are being tested in clinical trials either as sole therapy or in combination regimens are a liposomal PTX product (EndoTAG®-1), KRAS siRNA-loaded EVs and polymeric systems, liposomes for PKN3 siRNA delivery, liposomal IRT, DTX and PTX and micelle formulations of CPT and PTX. Targeted polymeric nanosystem composed of PLA-PEG units functionalized with PSMA loaded with DTX is also mentioned at Clinicaltrials.gov. Inorganic NPs are also being applied currently in clinical trials for diagnostic/imaging purposes. Clinical landscape of PC-targeted nanosystems has been reviewed elsewhere in detail [275].

Although nanosystem-laden CT dominates the clinical trials, new exciting trends are emerging which can possibly pave the way to next-generation PC therapies, including targeted therapies, molecular therapies, immunotherapies, cancer vaccines, stroma remodeling therapies, and metabolic therapies [276]. Currently, the main challenges associated with design, manufacture and commercialization of biomimetic nanosystem are:

(1) *Minimized immune recognition, biocompatibility and safety*. One of the main attributes of biomimetic nanosystems has to do with their bio-derived and biomimicking features ensuring extended blood circulation and biocompatibility. The presence of surface markers like CD47 enhance immune escape mechanisms of EVs, cell membrane-based nanosystems, whilst lipid coat on synthetic lipid membrane-coated nanosystems endow the nanosystems with colloidal stability and prolonged blood circulation profile. Regarding blood-derived protein NPs, their biocompatibility features are assured of their intrinsic biological origin. Depending on the complexity, degree of functionalization, method of preparation and source, some degree of immunogenicity and toxicity may emerge, and screening methods to rapidly evaluate the safety, immune recognition and biocompatible profile are key to successful development of biomimetic nanosystems, either of synthetic and natural origin.

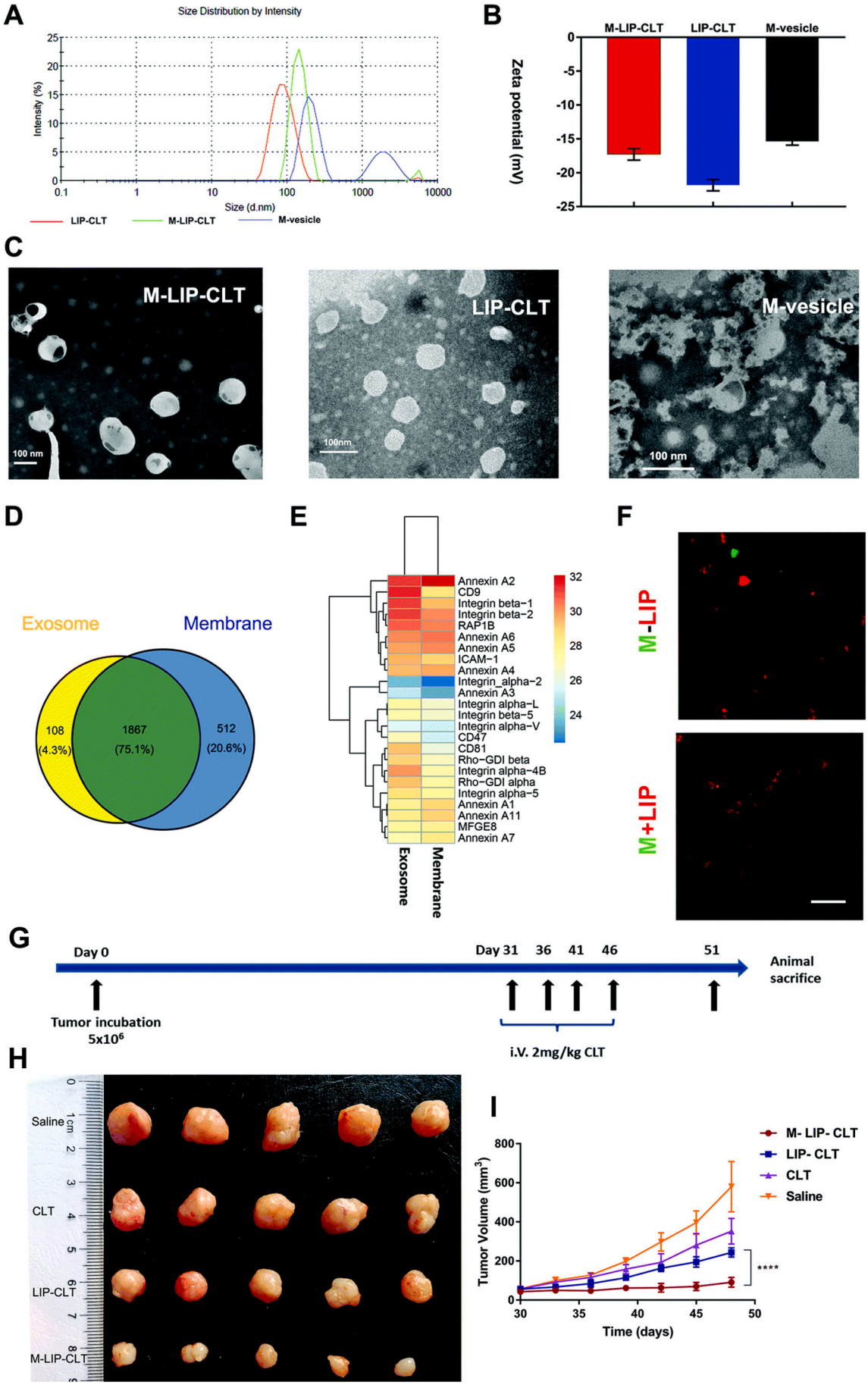

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Fig. 17. (A) Size distribution of celastrol-loaded control liposomes (LIP-CLT), hybrid celastrol-loaded PEGylated lipids with the DC2.4 cell membrane (M-LIP-CLT), and M-vesicle. (B) Surface charge of the formulations. (C) TEM pictures of the formulations. Scale bars = 100 nm. (D) Proteomic analysis or surface proteins on DC2.4 exosomes and DC2.4 cell membrane. (E) Heat map of relative proteins on DC2.4 exosomes and DC2.4 cell membrane. (F) Confocal fluorescence images of fused M-LIP and a physical mixture of lipids and cell membrane (red: lipids stained with DiD; green: cell membrane stained with PKH-26; scale bar: 50 μm). (G-I) *In vivo* antitumor efficacy and survival curves: (G) experimental design; (H) images of excised tumors on day 51; and (I) tumor volume analysis. Adapted with permission from [114]. Copyright Royal Society of Chemistry (2021). *Abbreviations:* M-LIP, membrane-liposome nanovesicle; CLT, celastrol. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(2) *Complex nature and characterization.* Protocols for preparing biomimetic nanosystems are complex and involve multiple steps for efficient manufacture of biomimetic nanosystems, especially the ones involving biological material. First, biological material such as cell membranes display tremendous complexity and variability in terms of abundance, classification and function of lipids and protein component, which can vary from cell to cell and offer difficulties for content quality and quantity control. Second, methods involving cell membrane extraction and coating onto NP cores are laborious and several external factors such as pressure, temperature, loss of sample, among others, interfere in the final yield in both quality and quantity. Hence, one of the main challenges of biomimetic nanosystems has to do with maintaining the reproducibility of the prepared batches to enable successful scale-up and translational potential, as discussed below. Another relevant issue consists in the yield of coating procedure of cell membrane-coated nanosystems, to several degrees: the information regarding obtainment of cell membrane coating is often overlooked, as in some cases the characterization is very sparse, and it is not possible to conclude that a successful coating was deposited on the NP core – other structures may be obtained, including fusion-related structures and the "coated" terminology is often used without sufficient characterization. Additionally, membrane extraction yield is often insufficient and may depend from cell type, and typical protocols involving cell membrane coating procedures resort only to protein-to-carrier weight ratio, which may offer an incomplete assessment, and the protein yield obtained is rarely mentioned in literature, together with lack of information regarding control of membrane extraction steps. It is also not clear how different cell sources can be more or less resistant to cell lysis procedures which can broadly impact overall membrane protein yield at the end of the membrane extraction process. Such coating success warrants additional information to the zeta potential and western blot analysis, as strongly negative ZP and evidence of protein expression by western blot mainly suggests biological cell membrane-derived structures are formed, not exactly that a successful coating was obtained. Moreover, artifacts may be formed on the surface of NP cores and TEM visualization may yield incorrect impression for a coating related to staining process [277]. Hence, correct identification and characterization of cell membrane coating is critical to ensure the quality of the manufacture process. The surface repertoire needs to be well characterizaed for efficient retention, integrity and functional activity, which also raises questions for stability over time, and clarifications regarding storage conditions and nanosystem stabilization methodology. Another point is the yield of the coating process, as such coating may be incomplete and further affect internalization of the coated nanosystem [278]. Recent articles have explored methodology to assess the extent of the coating procedure and calculate the coating yield, such as nanoplasmonics [279] and fluorescence measurements of dye-labeled membrane [278] which informs regarding the final structure obtained, the efficiency of the chosen membrane extraction and coating methods, and the potential internalization pathways at play when considering biomimetic systems. In order to improve the coating yield, a recent study explored inclusion of external lipids into cell membranes which could improve its fluidity and facilitate the fusion of membrane fragments, enabling a more effective reorganization towards improved coating process, as well as demonstrating improved targeting efficiency [280].

(3) *Better understanding of structure and function of biomimetic nanosystems and biointerfacing capabilities*. Although biomimetic nanosystems are endowed with enhanced pharmacokinetic profile on account of immune evading abilities and hydrophilic stealth, the underlying principles governing enhanced targeting capabilities still need further clarification. Homotypic targeting mechanism related to cell membrane-coated nanosystems dictating enhanced targeting to cancer cells needs further studies to clarify the key players and exact mechanisms underpinning tumor tropism and biodistribution, of utmost relevance to cell membrane-based nanosystems and EVs. This includes evaluating targeting specificity and efficacy. Another transversal issue has to do with the quality and preservation of surface repertoire, either biologically derived or synthetically made, on the efficacy of such biomimetic nanosystems to transverse biological barriers and engage with suitable cell receptors at the TME level. In the case of cell membrane-based nanosystems, membrane extraction, and subsequent sonication and extrusion steps may compromise the quality and quantity of the cell surface repertoire, and it is not clear in most studies the extent of correct spatial orientation of the cell membrane leaflets – right-side-in, right-side-out. According to the harshness of such processes, it is expected to have some degree of incorrect orientation which can further display unwanted consequences regarding biocompatibility, immunogenicity and safety of biomimetic nanosystems based on extracted cell membrane material. Other factors of relevance include ligand density, ligand distribution throughout the surface and underlying ligand-receptor binding mechanisms [281]. For instance, a recent study showed both rotational and translational movements are at play at the ligand-receptor binding interface and increase confinement as ligand density increases [281]. Besides the surface functionalization technological challenges, the emergent field of biomimetic nanosystems has seen innumerous application of nanosystems through different cancer types and strategies. It is still not fully clear the influence of the size, surface charge, morphology and protein corona formation of biomimetic systems, particularly cell membrane-based ones, on their *in vivo* fate, from systemic circulation to tumor biodistribution and uptake [282]. New studies comparing physicochemical and biochemical properties can be very useful to shine additional light on this matter [283]. Elasticity of cell membrane-coated nanosystems has been subject of further studies in which the degree of elasticity seems to impact pharmacokinetic profile. Moderate elasticity was suggested to enhance tumor accumulation, while softer, more elastic ones, exhibit the best performance regarding prolonged blood circulation [284]. Lastly, the interactions established between NP cores and cell membrane coating are also important to understand which NP cores are better suited to biomimetic coating and thus impacting overall stability and manufacturing [285]. Also of interest is the differential propensity of NP cores to be coated with biological membranes, and ways to improve the coating success and stability of the core-shell assembled biomimetic nanosystems are further warranted. A recent article explored the role of electrostatic interaction between cationic polymeric NP core with negatively-

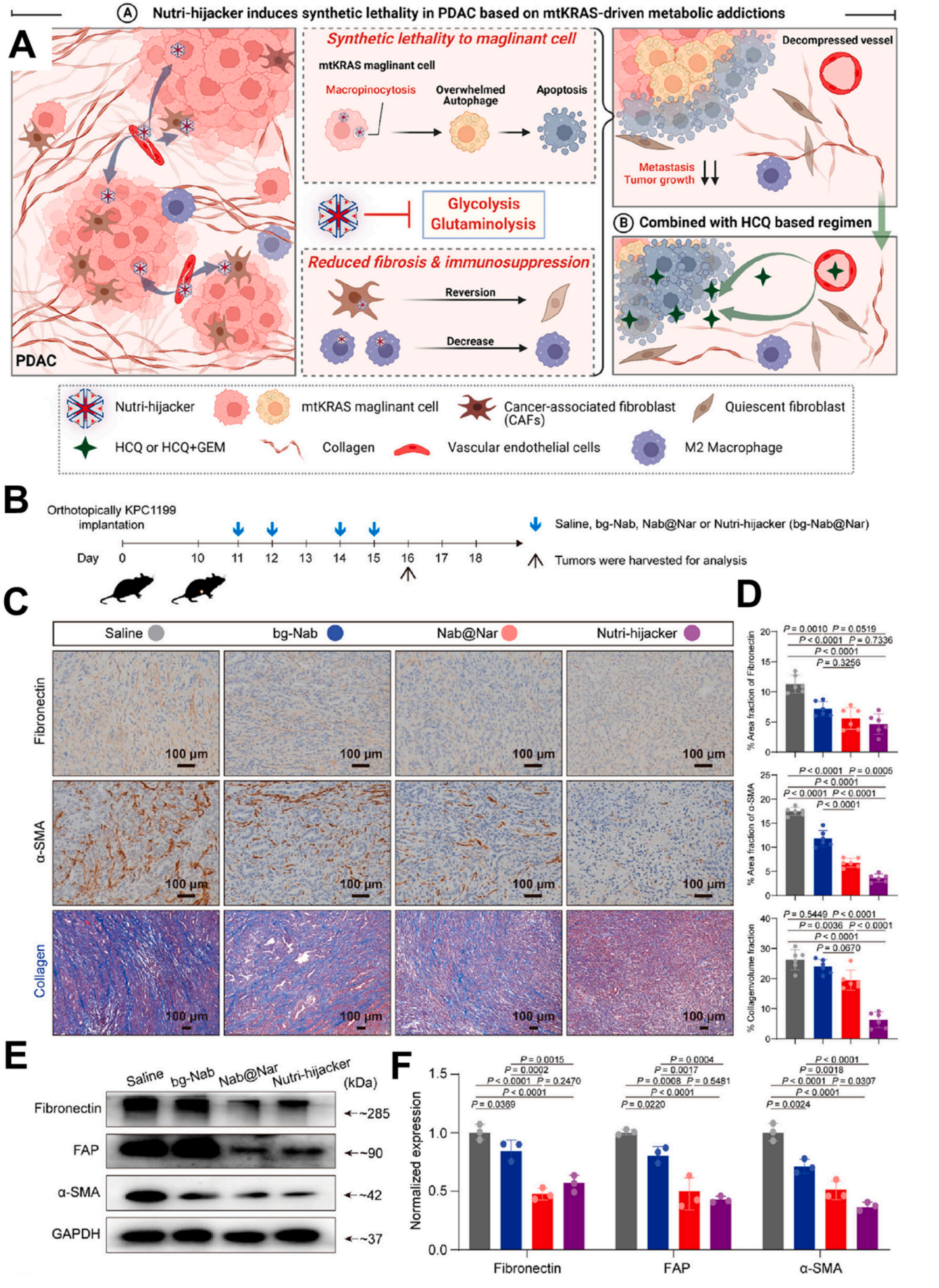

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Fig. 18. (A) Overview of the nutri-hijacker actuation on mtKRAS-driven metabolic addiction *via* glycolysis and glutaminolysis inhibition. (B—F) Nutri-hijacker reshaped TME *via* reducing tumor fibrosis and immunosuppression in PC. (B) Administration scheme in KPC1199 mice models. (C, D) Tumor slices stained for fibronectin, α-SMA and collagen and analyzed by ImageJ. ($n = 6$). (E, F) Analysis of expression of fibronectin, FAP, and α-SMA using Western blot. Adapted with permission from [269]. Copyright Elsevier (2023).

charged hybrid cell membrane, which suggested enhanced stability of the assembled structure, together with enhanced membrane binding affinity and rigidity which could be advantageous for *in vivo* applications [249], although other reports have initially concluded favorable coating procedure for negatively-charged NP cores due to electrostatic repulsion and maintenance of a well-defined biomembrane coating onto the negatively charged and hydrophobic surface of PLGA NP cores [285]. Also of interest is the comparison between EV-membrane coated nanosystems and cell membrane-coated nanosystems from same sources. While it is expected similar biocompatibility and targeting properties, cell membrane-coated nanosystems were suggested to display enhanced blood circulation and immune evading properties related to CD47 expression, leading to enhanced tumor biodistribution [273]. Another concerning aspect related to albumin and ferritin nanosystems has to do with their proteic nature and the necessity to understand better the self-assembly of protein-based building blocks in order to maximize cargo loading and stability. It is expected ferritin and albumin nanosystems may undergo additional developments regarding surface functionalization towards development of hybrid nanosystems for bolstered stability and surface targeting properties.

(4) *Clinical translation.* Despite the promising potential of biomimetic nanosystems in improving biocompatibility and targeting efficiency, significant hurdles have been raised regarding successful clinical approval and clinical translation. One of the most relevant steps has to do with scale-up and manufacturing process of EVs and cell membrane-based nanosystems [286]. Due to the complex biological and structural variability of these systems, suitable methods that ensure reproducibility at lab scale level may not be adequate for industrial scale production, and fine-tuning of the best strategy should be widely sought after, particularly in the case of cell membrane-based nanosystems that have not yet reached the market [190]. High manufacturing costs may limit the applicability of biomimetic systems, especially EVs and cell membrane-derived ones. Another issue is the lack of reproducibility as biological membrane sources and derived products display high variability, which limit consistency between batches. Several amendments can be made in this regard, such as the development of well-characterized and reproducible cell lines as membrane sources, together with improved validated protocols for controlling all manufacture steps from membrane extraction and purification, nanovesicles preparation and NP coating, including characterization. Production standardization is therefore a very key step to ensuring successful scale-up of engineered biomimetic nanosystems at the small scale. In the case of EVs, guidelines for isolation and characterization of EVs were already outlined, for instance, by Internation Society for Extracellular Vesicles (ISEV), which include standardized protocols ensuring consistency and reproducibility. Also relevant is the adaptability of lab-scale methods and equipment towards industrial scale production. In this regard, extrusion procedures may be more advantageous for industrial scale manufacturing of cell membrane-based nanosystems, as opposed to sonication. When compared with naturally occurring MSC-derived EVs and their obtainment, MSC membrane extrusion showed similar features at the same time leading to higher yields, quality maintenance and fastened manufacturing suitable for large scale production [287]. Other study compared EVs with cell membrane nanovesicles derived from glioblastoma tumor cells, showing negligible immunogenicity, similar *in vivo* immune profile, demonstrating cell membrane nanovesicles as scalable, safe and efficient alternatives to their EV counterparts [288]. EVs can also be used as membrane material [289] and are endowed with some advantages when compared to cell membrane-coated nanosystems as the biomimetic structure is already formed through cell secretion processes, and evidence the right orientation of surface repertoire molecules, and may show reduced immunogenicity while maintaining targeting abilities, and are also devoid of contamination residues like nuclear material, organelles and undesired proteins. A recent study explores density gradient centrifugation for concentration of lipid layers which could improve the coating procedure of lipid bilayers around NP cores [290]. Another method reports on production of endogenously-secreted membrane-coated NPs, by taking advantage of cells natural biological processes, namely trafficking of cell-secreted vesicles. In this case it is possible to obtain already coated structures without the need to isolate cell membrane material and prepare the coating off NP cores with the cell membrane material [291]. Other methods that may improve the scalability of cell membrane-coated nanosystems are flash precipitation [292], microfluidic [293], microfluidic sonication [294] and microfluidic electroporation [295], which comprise more suitable automated and high throughput methods with easier implementation in an industrial setting. The manufacture of biomimetic nanosystems will also benefit of development of quality-by-design protocols to maximize efficiency of the process of preparation of the engineered biomimetic nanosystems in a timely, cost-effective manner by exploring the influence of a plethora of variables influencing the manufacture process [296]. Finally, purification of biomimetic nanosystems is a key challenge and should also be addressed in order to guarantee removal of organic solvents used in the preparation of NP cores, albumin and ferritin nanosystems, and immunogenic material and non-assembled membrane coatings around NP cores [297]. Another challenge that nanosystems face has to do with regulatory issues, which may face complex regulatory framework. The optimization of manufacture methods together with improved safety of nanomaterials may help leveraging their clinical potential and facilitate approval by regulatory agencies [298]. Above all, the manufacture of biomimetic nanosystems should comply with good manufacturing practices (GMPs). Lack of specific regulatory guidelines may restrain clinical translation. The regulatory hurdles may be partially solved by early engagement with regulatory authorities to assess critical validation of manufacture, characterization, quality control and safety guidelines.

(5) *Therapeutic scope.* Nanosystems are promising platforms for advanced and multimodal PC therapeutics, and have leveraged delivery of CT, nucleic acid therapy, stroma therapy, phototherapy, IT and targeted therapies, often in combination. Novel drug combinations with synergic activities and ratiometric loading may also constitute interesting avenues to tackle PC pathology at several fronts, and nanosystems enable co-encapsulation of two, three or more drugs at the same time with site-specific release and fine-tuned pharmacokinetics. Furthermore, the versatility of nanosystems has enabled to devise advanced targeting strategies, either by targeting ligands or by exploring stimuli-responsive payload release. Particularly, exciting results were obtained in PC IT, stroma remodeling and

Table 9
Examples of nanomedicines in clinical trials for PC therapy and approved nanomedicines employed in PC therapy.

Nanosystem	Drug	Phase	Status	Name	Identifier[a]
Nanoparticle	CUR + DOX	I, IIa	Active	Imx110	NCT03382340
Inorganic hafnium oxide	–	I	Recruiting	NBTXR3	NCT04484909
AGuIX-NP	–	I/II	Recruiting	Nano-SMART	NCT04789486
Albumin NPs	PTX	Approved	–	Abraxane®	–
mPEG-PLA	PTX	Approved	–	Genexol-PM®	–
Liposome	DOX	II	Terminated	Doxil®	NCT00426127
PEGylated liposome	IRT	Approved	–	Onivyde®	–
Liposome	PTX	III	Completed	EndoTAG® -1	NCT03126435
MSC-derived EVs	KRAS G12D siRNA	I	Active	iExosome	NCT03608631
Polymeric matrix	KRAS siRNA	II	Unkonwn	siG12D LODER	NCT01676259
Liposome	BikDD	I	Withdrawn	BikDD NP	NCT00968604
Liposome	PTX	IV	Unkonwn	–	NCT04217096
Liposome	DTX	II	Completed	Taxotere®	NCT01186731
Liposome	IRT	II	Completed	PEP02	NCT00813163
Micelles	CPT	III	Completed	NC-6004	NCT02043288
Micelles	PTX	II	Recruiting	–	NCT06199895
Liposome	PKN3 siRNA	I/II	Completed	Atu027	NCT01808638
CD	siRNA	I	Terminated	CALAA-001	NCT00689065
CD	CPT	I/II	Completed	CRLX101	NCT00333502
PLA-PEG-PSMA	DTX	I	Completed	BIND-014	NCT01300533
Nanoparticle	PTX	I	Completed	Nanotax	NCT00666991
SNALP	PLK1 siRNA	I	Completed	TKM-080301	NCT01437007

[a] In which the NP intervenes. Some formulations are already clinically approved for other cancer type-related treatments, and are incorporated in the clinical PC context in association with other drugs.

CT and their interconnected mechanisms. Alternative administration routes may offer interesting opportunities to improve patient compliance and safety, such as oral administration [299].

(6) *Advancing models of disease, tumor heterogeneity and patient stratification.* Further advancements are needed to build suitable models able to recapitulate more closely the complexity of PC TME for testing nano-based PC therapies [300–302], such as PC organoids [303], as well as new breakthroughs in personalized medicine such as 3D bioprinting [304,305]. Further research to improve PC biology and genetics knowledge is urgently called for with special emphasis on crosstalk established between PC cells, stroma cells (CAFs, immune cells, stem cells, vasculature, and neural tissue) and tumor microbiota. As tumors, including PC, have high phenotypic and genotypic heterogeneity, a more personalized approach based on patient stratification can help selecting the patients that would benefit more from each treatment and also help clinical translation of the nanosystem. This could also help address any emerging immunological variability responses among different treated individuals through immune profiling. Another major challenge consists of the difficulty of extrapolating results from *in vitro* to *in vivo* setting and to the full landscape of human clinical testing, which is further undermined due to the complexity of the *in vivo* barriers. It is possible that major breakthroughs in artificial intelligence and machine learning approaches may expedite clinical translation by means of accelerated data analysis, timely screening methods and providing novel cues to whether the engineered biomimetic nanosystems are suitable or not for the application they are designed for.

(7) *Delayed toxicity.* While biomimetic nanosystems offer advantages such as extended blood circulation half-life and targeted delivery, these same features may also lead to delayed responses that are not necessarily beneficial. In particular, prolonged circulation and tissue accumulation can result in delayed immunotoxicity and organ-specific toxicity. To date, these risks have been underexplored, as most *in vivo* studies have assessed these systems over relatively short timelines, potentially overlooking long-term adverse effects. Unanticipated immune reactions and organ toxicity—especially under long-term or multidose regimens—warrant thorough investigation. This calls for well-designed animal studies that evaluate long-term administration, immune-related risks, comprehensive biodistribution, and organ-specific toxicity over extended periods to identify potential harm.

5. Conclusion

PC is a highly lethal and aggressive malignancy, currently one of the leading causes of cancer-related deaths worldwide, in both men and women. PC is known to be highly resistant to standard CT. It is characterized by an immunosuppressive and hypoxic TME and is surrounded by a dense desmoplastic stroma compartment that limits drug accessibility and perfusion. Although standard CT is one of the main therapeutic strategies for PC management contributing to tumor eradication by a cytotoxic effect, CT is associated with a poor pharmacokinetic profile and triggers deleterious systemic toxicity which broadly compromise the efficacy and safety of PC treatment. Additionally, the underlying barriers of PC and TME vastly undermine response to more innovative modalities, such as IT and cancer vaccines. This concerning scenario urgently calls for innovative and highly specific therapeutic strategies to counteract the urgent clinical challenge.

Nanotechnology, through the use of nanosystems, appears as a reliable solution, offering several precision materials for cancer used to build drug delivery nanosystems, translated in overall improvements in safety and therapeutic efficacy. These include lipid-based, polymer-based (*e.g.* micelles, PLGA NPs, hydrogels, etc), peptide/protein-based, inorganic-based, hybrid-based and carrier-free nanosystems. Although nanosystems may help improve drug stability, blood circulation, and minimize systemic cytotoxic effects by improving their tumor accumulation and enabling controlled release of drugs, several drawbacks still persist, such as the lack of both biocompatibility and targeting features.

In the last few years increased attention has been paid to biomimetic nanosystems that can mimic either partially or totally biological systems, including lipid layers as suitable stealth coatings mimicking the composition of cell membranes, and cell membrane-derived vesicles, such as exosomes, cell membrane nanovesicles and cell membrane-coated nanosystems which display intrinsic cancer-targeting abilities, enhanced biocompatibility, decreased immunogenicity and a prolonged blood circulation profile.

CRediT authorship contribution statement

Miguel Pereira-Silva: Visualization, Validation, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft. **Francisco Veiga:** Supervision, Resources, Project administration, Funding acquisition, Formal analysis, Conceptualization, Writing – review & editing. **Ana Cláudia Paiva-Santos:** Supervision, Resources, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. **Angel Concheiro:** Supervision, Project administration, Investigation, Funding acquisition, Conceptualization, Writing – review & editing. **Carmen Alvarez-Lorenzo:** Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare no conflict of interest.

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Data availability

No data was used for the research described in the article.

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