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ADVANCED REVIEW

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Bioinspired soft nanovesicles for site-selective cancer imaging and targeted therapies

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Abstract

Cell-to-cell communication within the heterogeneous solid tumor environment plays a significant role in the uncontrolled metastasis of cancer. To inhibit the metastasis and growth of cancer cells, various chemically designed and biologically derived nanosized biomaterials have been applied for targeted cancer therapeutics applications. Over the years, bioinspired soft nanovesicles have gained tremendous attention for targeted cancer therapeutics due to their easy binding with tumor microenvironment, natural targeting ability, bioresponsive nature, better biocompatibility, high cargo capacity for multiple therapeutics agents, and long circulation time. These cell-derived nanovesicles guard their loaded cargo molecules from immune clearance and make them site-selective to cancer cells due to their natural binding and delivery abilities. Furthermore, bioinspired soft nanovesicles prevent cell-to-cell communication and secretion of cancer cell markers by delivering the therapeutics agents predominantly. Cell-derived vesicles, namely, exosomes, extracellular vesicles, and so forth have been recognized as versatile carriers for therapeutic biomolecules. However, low product yield, poor reproducibility, and uncontrolled particle size distribution have remained as major challenges of these soft nanovesicles. Furthermore, the surface biomarkers and molecular contents of these vesicles change with respect to the stage of disease and types. Here in this review, we have discussed numerous examples of bioinspired soft vesicles for targeted imaging and cancer therapeutic applications with their advantages and limitations. Importance of bioengineered soft nanovesicles for localized therapies with their clinical relevance has also been addressed in this article. Overall, cell-derived nanovesicles could be considered as clinically relevant platforms for cancer therapeutics.

This article is categorized under:

Biology-Inspired Nanomaterials > Nucleic Acid-Based Structures

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KEYWORDS

nanoCells, nanoTheranostics, nanovesicles, targeted therapy

1 | INTRODUCTION

Over the years, numerous nanobiotechnology (Bindra et al., 2021; Huang et al., 2018; Jain et al., 2021; Patel et al., 2022; Shi et al., 2017) and cellular-based therapeutic strategies (Basar et al., 2020; Findeisen et al., 2021; Fischbach et al., 2013; Ullah et al., 2015; Yu et al., 2020) have been applied for targeted cancer therapy although the cost of treatment is rising continuously (J. Herrmann, 2020; Schmidt et al., 2020; Vokinger et al., 2020). Systemic administration and delivery of therapeutic probes viz., anticancer drugs on target site have been affected by off-targeting that lead to design of localized therapies with low efficacy and high toxicity (Genard et al., 2017; Pich et al., 2019; Van der Jeught et al., 2018; Vokinger et al., 2020; Ward et al., 2020). Evolving site-specific therapeutic strategies to assist localized and triggered drug delivery embrace significant impact for reducing toxicity, nonspecific targeting, and unwanted death of surrounding healthy cells (Deng et al., 2019; Goodman et al., 2017; Jain et al., 2020; Z. Qi et al., 2020; Srinivasarao & Low, 2017; Wang, Li, & Nie, 2021; X. Xu et al., 2017). In the past decades, a large body of biomedical researchers has focused to understand the biological barriers and targeting strategies of administered nanobiomedicines (Fenton et al., 2018; Khan et al., 2021; Talebian et al., 2021; van der Meel et al., 2019). But, the targeted therapeutic mechanism, specific bio-distribution, and pathways of site-selective tumor accumulation of injected nanosized biomaterials and soft vesicles are unknown, which hamper their clinical trials and Food and Drug Administration (FDA) approval (Bernal et al., 2021; J. Cao et al., 2020; de Lázaro & Mooney, 2021; Y. Li et al., 2021; Mirkasymov et al., 2021; Nayak et al., 2021; van der Meel et al., 2019; Y. Wang, Gou, et al., 2021; Zielonka et al., 2017). Hence, conventional treatment strategies like chemotherapy, radiation therapy, and surgery are being practiced heavily even today (B. Chen et al., 2018; Jeremić et al., 2021; Matsumoto et al., 2021; Thompson et al., 2018). Remarkably, the slow progress of developing advanced treatment methodologies force us to depend on these conventional therapeutic approaches that require multiple and heavy doses of therapeutic agents along with high energy of electromagnetic radiations (P. Hu, Hou, et al., 2021; Ke & Shen, 2017; V.-N. Nguyen et al., 2020; Xin et al., 2017). These aforementioned parameters remain as major concerns of these traditional treatment modalities exhibiting various side effects (Redd et al., 2021; Q. Zhao, Liu, et al., 2020). Apart from these limitations, whole-body circulation and nonspecific bio-distribution, poor targeting and low penetration in tumor environment, easy and quick excretion, organ toxicity, namely, liver cirrhosis, cardiotoxicity, and nephrotoxicity are other critical issues of administered therapeutic probes (Chaa et al., 2021; Oun et al., 2018; Shah et al., 2018; X. Zhang et al., 2017).

Reliability of conventional treatment strategies to treat cancer patients is losing pace every day, hence, designing a safe and cost-effective treatment strategy has become a priority to reduce disease allied deaths globally (Kelak et al., 2018). To overcome the above-highlighted hurdles, numerous surface engineered tinny sized "nanomedicines" such as plasmonic gold nanoparticles, polymeric nanospheres, graphene oxide sheets, porous silica particles, gold-silica hybrid structures, drug conjugated self-assemblies, and so forth have been proposed for cancer imaging and therapeutic applications (Chauhan et al., 2019; Gonçalves et al., 2020; Lerra et al., 2019; Li Volsi et al., 2017; Mehta et al., 2021; Ren et al., 2020; Selvaraj et al., 2018; Y. Wang, Wang, et al., 2018; Wen et al., 2021). However, sophisticated synthesis and surface engineering, low cargo capacity, slow biodegradation, poor biocompatibility, lack of site-selective drug delivery response, easy absorption of protein molecules on their surface during blood circulation, major accumulation in liver and spleen, low penetration, and retention ability in tumor environment are critical obstacles of these nanostructures (Bailly et al., 2019; Cai & Chen, 2019; Chinen et al., 2017; Farjadian et al., 2019; Kramer et al., 2017; J.-Y. Lin, Lai, et al., 2020; Moghimi & Simberg, 2018; Riedel et al., 2020; Selvaraj et al., 2018; Sindhwani et al., 2020; Stepien et al., 2018; M. Xu et al., 2018). Thus, lipid self-assembled nanosized structures named liposome have been proposed as a safe cargo carrier with better biocompatibility, biodegradation ability, high, and multiple cargo (hydrophilic, hydrophobic, and amphiphilic) loading capacity (Al-Ahmady & Kostarelos, 2016; Fan et al., 2021; Lakkadwala & Singh, 2019; Panahi et al., 2017). As of now, various lipid-based formulations have been developed for cancer diagnosis and therapeutic applications at preclinical level and clinical level (Bulbake et al., 2017; Lamichhane et al., 2018; M.-K. Lee, 2019; Pattni et al., 2015; Wood et al., 2021). Nevertheless, rapid protein corona formation on liposomal surface and their fragile nature make them nonspecific towards cancer cell/tumor and premature release of loaded cargo molecules, respectively (Caracciolo, 2018; Caracciolo et al., 2014; Giulimondi et al., 2019; Palchetti et al., 2016; Pozzi et al., 2014).

Recently, cell-derived nanosized vesicles "bioinspired soft nanovesicles" such as exosomes, extracellular vesicles, cell ghosts structures, and so forth have been proposed as versatile carriers of therapeutic biomolecules (Gurunathan et al., 2019; I. K. Herrmann et al., 2021; Kalluri & LeBleu, 2020; Ma et al., 2021; Pozzi et al., 2014; Singaravelu et al., 2020). These systems are excellent therapeutic candidates due to high biocompatibility, easy preparation, inherent targeting surface markers, specific bio-distribution and selective targeting ability, and improved stability (Abello

et al., 2019; Betzer et al., 2020; I. K. Herrmann et al., 2021; Malhotra et al., 2019; Parodi et al., 2013; Raposo & Stahl, 2019). Abundance of natural targeting biomolecules on the surface of these biological nanostructures inhibits the protein corona formation which improves the blood circulation time, stability, and site-selective targeting of cancer cell/tumor (H. Y. Chen, Deng, et al., 2020; Corbo et al., 2016; Mahmoudi et al., 2016; Mosquera et al., 2020; Rao et al., 2017; Xia et al., 2019). However, low product yield, poor reproducibility, and uncontrolled particle size distribution have remained as major challenges of these platforms (D. Yang et al., 2020). These biological soft nanovesicles are different from each other at their molecular level mainly with the presence of surface proteins, markers and nucleic acid (Ailuno et al., 2020; Doyle & Wang, 2019; Krishnamurthy et al., 2016). For example, hypotonic treated cells followed by sonication/or extrusion derived nanoszied vesicles are loaded without any nucleic acid, whereas, cell released exosomes are loaded with nucleic acids (Armstrong et al., 2017; X. Han et al., 2019; Le et al., 2021). Naturally available surface biomarkers and soft nature of these nanosized vesicles make them easy to communicate with cancer cells and its interior within the tumor microenvironment (Cheung et al., 2018; Kikuchi et al., 2019; Schatz & Vardi, 2018). Hence, soft vesicles are able to deliver their loaded cargo molecules, namely, anticancer drugs, tumor growth inhibitors, genes, and nucleic acids (miRNAs, mRNAs, and DNA) at the particular site of the tumor or cancer cells (Duan et al., 2021; Elsharkasy et al., 2020; Joshi et al., 2020; Jurgielewicz et al., 2021; Q. Lin, Zhou, et al., 2020).

Successively, these therapeutic engineered soft nanovessels inhibit the rapid growth of new blood vessels and dense vascularization in heterogeneous tumor areas by reducing the proliferation of endothelial cells, cut down of oxygen and nutrients supply (D. Chen, Qu, et al., 2020; P.-J. Gong et al., 2020; S. Hu, Ma, et al., 2021; M. Liu, Hu, & Chen, 2020; Ural et al., 2021; Ying et al., 2021). To the best of our knowledge, these vesicles are easily penetrable in heterogeneous tumor environments for durable binding and long-time retention due to their biological nature, inherently available surface biomarkers, and soft nature (Khalife et al., 2020; Khani et al., 2021; Y. Li et al., 2019). Therefore, these biologically derived particles demonstrate their significant performance in biological therapeutics (Jiang et al., 2019, 2021; Plebanek et al., 2017; Rao et al., 2020; Q. Zhao, Hai, et al., 2020). Overall, this review focuses on the recent developments of cell-derived nanovesicles for targeted imaging and cancer therapeutics. Major advantages and clinically acceptable approaches with various examples of these biological hybrids have been discussed briefly.

2 | CELL-DERIVED VESICLES

Cell-derived vesicles have been documented as potential circulating cancer biomarkers which have shown their deep intercellular communications (Becker et al., 2016; Lane et al., 2018; Paolicelli et al., 2019; Rak & Guha, 2012). Bioinspired extracellular vesicles (EVs) "exosomes" contain phospholipid membrane with heterogeneous distribution secreted by variety of mammalian cells (Juan & Furthauer, 2018; Margolis & Sadovsky, 2019). Phosphatidylcholine and sphingomyelin are majorly distributed in the outer layer of cell-derived vesicles membrane, whereas, the inner layer is largely designed with phosphatidylserine and phosphatidylethanolamine. Initially, these vesicles were named as cell dust, but now they are stable sources of circulating biomarkers and can transport various molecules such as proteins, mRNA/miRNA, DNA, and so forth (Juan & Furthauer, 2018; Margolis & Sadovsky, 2019; Pucci et al., 2016; Shao et al., 2018; Skog et al., 2008). Several routes for extracellular vesicles formation have been reported in the literature, but the exact mechanism is not clear so far.

Based on the biogenesis process, these EVs have been classified into three categories such as exosomes, microvesicles, and apoptotic bodies (Shao et al., 2018). Among them, exosomes have been highlighted as a unique platform for cancer biomedicine applications (Gyorgy et al., 2011; Shao et al., 2018; Tamura et al., 2021). Exosomes are the form of small membrane vesicles having a particle size in the range of 30–150 nm secreted by various cells during cellular exocytosis process followed by endocytic pathway that can stimulate immune responses at preclinical or clinical level (H. Rashed et al., 2017; Pullan et al., 2019). Peripheral and transmembrane proteins are major components of exosomes (Pullan et al., 2019). Biogenesis of exosomes has the following steps: (a) formation of secretory endosome from cytoplasmic membrane, (b) formation of intraluminal vesicles "loaded inner buds" within the endosome known as multivesicular body (MVB), (c) maturation of late endosomes, and (d) extracellular release of intraluminal vesicles "exosomes" followed by plasma membrane fusion (Gyorgy et al., 2011; H. Rashed et al., 2017; Pullan et al., 2019; Shao et al., 2018; Tamura et al., 2021; Figure 1). Due to the presence of important components like proteins, lipids, nucleic acids, and so forth, these cell-derived exosomes demonstrate their major role in biological processes (Shao et al., 2018). Mostly all body fluids, namely, saliva, breast milk, blood, and urine exhibit exosomes that play an important role in cell to cell communication by transporting protein, RNA, DNA, lipid, and so forth (de la Torre Gomez et al., 2018; Y. Han,

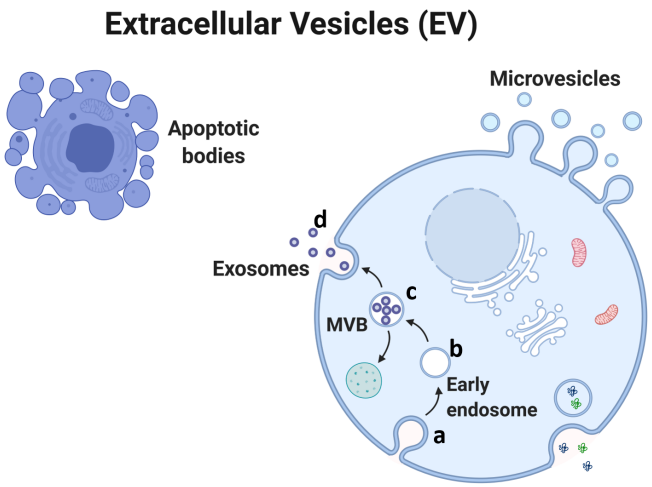

FIGURE 1 Biogenesis and secretion of cell-derived extracellular vesicles (EVs) followed by outward budding of plasma membrane (microvesicle pathway) inward budding of endosomal membrane (exosome pathway). Exosomes are vesicle products of endocytic origin from the inward invagination of the plasma membrane to the early endosome

Jia, et al., 2018; M. Li et al., 2014; Shao et al., 2018). It should be noted that exosomes comprise a variety of substances like specific proteins, lipids, DNA, mRNA, and noncoding RNAs (Shao et al., 2018).

In the past several years, various research groups have explained the promising applications of exosomes in biomedical research along with their secretion procedures (de la Torre Gomez et al., 2018; Gyorgy et al., 2011; H. Rashed et al., 2017; Y. Han, Jia, et al., 2018; M. Li et al., 2014; Pullan et al., 2019; Shao et al., 2018; Tamura et al., 2021). Cell-derived extracellular vesicles (EVs) and their structural components are characterized by microscopic methods with their physical features like surface morphology, vesicle size, and distribution as shown in Figure 2a–f (M. Li et al., 2014; Rupert et al., 2017; Shao et al., 2018; Szatanek et al., 2017; Tiwari et al., 2021).

Electron microscope and atomic force microscope (AFM) have been predominantly applied to study the morphology and distribution of these extracellular vesicles. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are well-established and useful techniques in extracellular vesicles (EVs) research for analyzing their 3D surface topography information, elemental composition, and molecular understanding at nanoscale (Shao et al., 2018; Sharma et al., 2018; Tiwari et al., 2021). Notably, the round morphology of isolated extracellular vesicles substructures and their variable constitutive elements, namely, lipid, surface markers, and proteins are easily characterized by Cryo-Electron Microscopy (cryo-EM, at very low temperature of $-100^{\circ}C$) and AFM (using mechanical cantilever; Shao et al., 2018; Sharma et al., 2018). On the other hand, Dynamic Light Scattering (DLS) is another promising technique to measure the physical attributes of EVs in the suspension phase under monochromatic light illumination (Palmieri et al., 2014; Shao et al., 2018; Varga et al., 2020). In DLS, during Brownian motion, the scattered light from constructive and destructive interferences of EVs fluctuates with the intensity which converts to the diffusion rate of the particles for determining the hydrodynamic diameter (Shao et al., 2018; Varga et al., 2020). Light microscopic-based single extracellular vesicle analysis (SEA) technique is a recent achievement (Shao et al., 2018). The single extracellular vesicle methodology is a robust technique for measuring protein biomarker in distinct vesicles followed by immuno-stained microfluidic chamber where vesicles are immobilized on the chip and obtained signal-to-noise ratio are usually much higher than the free-floating vesicles under flow condition (Shao et al., 2018). Extracellular vesicle as explained in Figure 2e,f (K. Lee et al., 2018; Shao et al., 2018). However, these EVs are heterogeneous in their size, in terms of their origin and molecular components (Shao et al., 2018).

Recently, ultracentrifugation, polymer-based precipitation, and fluidic systems have been developed to enhance EVs isolation processes as highlighted in Table 1 (Shao et al., 2018). Apart from the isolation methods, protein and biomarkers analysis of these extracellular vesicles (EVs) have become prior important to utilize these extracellular vesicles for biomedical applications such as bio-sensing, bio-imaging, cell-based therapeutics, targeted drug delivery, biological therapy, and so forth (Chin et al., 2020; Bose et al., 2018; Latifkar et al., 2019; K. Lee et al., 2018; Shao et al., 2018; Sharma et al., 2021; Tran et al., 2020; Verweij et al., 2021). Importantly, extracellular vesicle proteins are mainly derived from the cellular membrane and cytosol, but not from intracellular organelles such as endoplasmic reticulum, Golgi apparatus, and nucleus (Latifkar et al., 2019; Shao et al., 2018). The International Society for Extracellular Vesicles

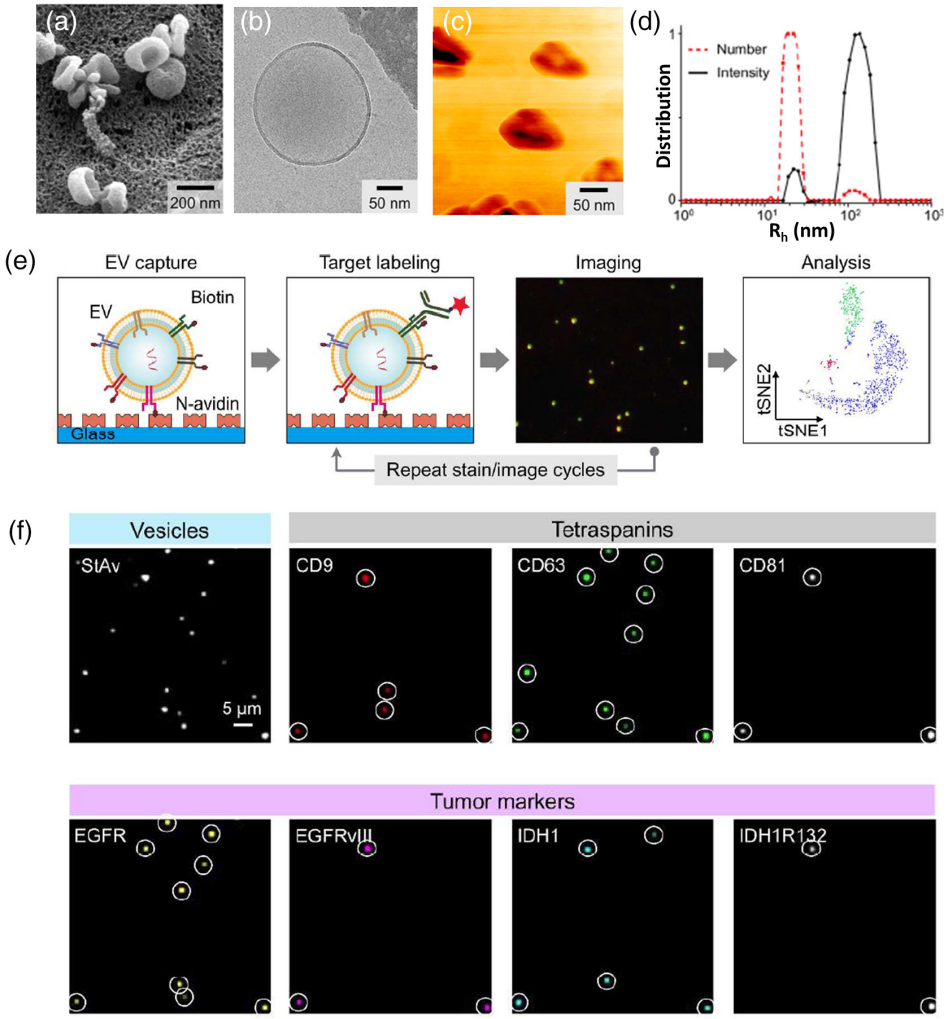

FIGURE 2 (a) 3D surface topography measure by scanning electron microscopy (SEM), (b) Cryo-electron microscopy (cryo-EM), (c) atomic force microscopic images, and (d) dynamic light scattering (DLS) measures of extracellular vesicle. Single extracellular vesicle analysis (SEA), (e) biotinylated and captured extracellular vesicle on a flat surface coated with neutravidin (Av) followed by staining with fluorescent antibodies (fluorophores are quenched and the staining process is repeated for a different set of markers for the analysis). For example, SEA image analysis, (f) Gli36-WT cell-derived extracellular vesicles are biotinylated and captured. The single extracellular vesicle is detected by staining with fluorescent streptavidin StAv (top left). For molecular profiling, extracellular vesicles are stained for pan-EV markers (tetraspanins; CD9, CD63, and CD81) and tumor markers (EGFR, EGFRvIII, IDH1, and IDH1R132). Each circle indicates individual extracellular vesicles. Reproduced with permission from American Chemical Society (K. Lee et al., 2018; Shao et al., 2018)

(ISEV) recommends specific characterization protocols to examine extracellular vesicle proteins mainly for transmembrane and cytosolic proteins (Latifkar et al., 2019; Shao et al., 2018). Mammalian cells derived vesicles are mainly distributed with transmembrane and lipid attached extracellular proteins largely (Latifkar et al., 2019; Salunkhe et al., 2020; Shao et al., 2018; Tran et al., 2020; Y. Wang et al., 2019).

In the obtained vesicles, these transmembrane proteins are augmented with tetraspanins named CD9, CD63, and CD81 which are involved in membrane trafficking (Mathieu et al., 2021; Salunkhe et al., 2020; Shao et al., 2018). On the other hand, these EVs are supplemented with CD40 ligands and other specific transmembrane protein receptors like epithelial cell adhesion molecule/EpCAM, epidermal growth factor receptors/EGFRs, and so forth (Al-Nedawi et al., 2009; Graner et al., 2009; Shahir et al., 2020; Shao et al., 2018; Xiong et al., 2021).

Western blotting, enzyme-linked immunosorbent assay (ELISA), and mass spectrometry are widely used conventional methods for protein analysis (Shao et al., 2018). However, these procedures typically require a large sample volume, long time, wide processing, and dedicated instrumentation that limit their clinical uses (Shao et al., 2018). To address the critical technical encounters of these methodologies, new methods for protein quantification and sensing

TABLE 1 Methods of isolation for extracellular vesicles (Shao et al., 2018)

Name of isolation technique	Isolation mechanism	Advantages	Disadvantages	Remarks
Ultracentrifugation	Based on density	1. Gold standard 2. Established protocol	1. Long time (>4 h) 2. Large sample volume 3. Low recovery and purity	requires ultracentrifuge
Sucrose-gradient centrifugation	Based on density	1. Gold standard 2. High purity	1. Long time (>4 h) 2. Large sample volume 3. Low recovery	Requires ultracentrifuge
Co-precipitation	Based on surface charge	1. Easy in use 2. User-friendly processing	Low scalability	lack of specificity
Chromatography	Based on molecular weight	1. High yield 2. Wide variety of eluents	Low scalability	lack of specificity
Field flow fractionation	Based on the size and molecular weight	1. Broad separation range 2. Wide variety of eluents	Long time	Requires fractionation equipment

are in the developing stage (C. Chen et al., 2010; Z. Zhao et al., 2016). These newly proposed methods are significantly based on the molecular contents of extracellular vesicles which require smaller sample volumes and minimum processing time (C. Chen et al., 2010; Reategui et al., 2018). Second, small particle flow cytometry is a promising technique to characterize the single cells or micrometer-sized ghost cellular entity that is based on the light scattering and fluorescence stimulation (Shao et al., 2018; Stoner et al., 2016). This is highly sensitive technique that can distinguish small particles with 100 nm in diameter where different fluorescent probes and labeling protocols have been applied for staining the vesicle membrane and surface markers (Nolte et al., 2012).

Next, Magnetic Nanoparticles (MNPs) based sensing protocols have gained considerable attention which is little snooping from native biological samples (Shao, Min, et al., 2012). These targeted magnetic nanoparticles can turn an optically turbid samples to transparent due to magnetic fields and high contrast in the inherent biological background (Shao et al., 2018; Shao, Min, et al., 2012). During nuclear magnetic resonance (NMR), these magnetic nanoparticles create local magnetic fields with different transverse relaxation rate of surrounding water molecules to increase the analytical signal. Hence, nanoparticulate NMR-based technique represents a smart sensing procedure with low sample volume and processing time that could be considered as a versatile approach for detecting circulating tumor cells and markers from the blood samples (Shao et al., 2018). In the case of cell-derived extracellular vesicles detection, these NMR-based technologies have various engineering challenges due to small size of vesicles (Shao et al., 2018; Shao, Min, et al., 2012). Further, a two-step bio-orthogonal click chemistry approach has also been recognized as a promising technique to examine and label the extracellular vesicles with magnetic nanoparticles (MNPs; Shao et al., 2018; Shao, Chung, et al., 2012). This approach improves the effectiveness of small molecule (<200 Da) labeling while retaining the targeted vesicles without changing the size of the antibody or the MNPs (Shao et al., 2018). Profusion of extracellular vesicle biomarkers from targeted extracellular vesicles are directly measured on a microfluidic micronuclear magnetic resonance (μNMR) chip. Importantly, this technique is about 10^3-fold sensitive compared to Western blotting and ELISA testing (Shao et al., 2018).

Apart from this approach, surface plasmon resonance (SPR) based nanoplasmonic exosome sensor has recently been developed that represents a novel label-free characterization of extracellular vesicles (Brolo, 2012). In this technique, the local refractive index of biomolecules attached metal–dielectric interface changes under light irradiation followed by the collective oscillation of conduction electrons at the metal-dielectric interface which is 10^4 and 10^2 fold sensitive than Western blotting and ELISA, respectively (Brolo, 2012; Shao et al., 2018). This process can be completed within <30 min with a minimal volume of samples. Integrated Magnetic-Electrochemical exosome (iMEX) and

ExoScreen methodologies are also recently developed approaches for rapid EV analysis (Jeong et al., 2016; Shao et al., 2018; Yoshioka et al., 2014). iMEX technique (Jeong et al., 2016) demonstrate the isolation of cell-specific exosomes without any filtration or centrifugation with better detection ability through magnetic and enzymatic amplification and electrical detection stimulation. Whereas ExoScreen technique (Yoshioka et al., 2014) is based on the luminescent liquid biopsy with homogeneous evaluation of EVs followed by donor beads: singlet oxygen release under 680 nm excitation and acceptor beads: to detect the emission at 615 nm obtained from released singlet oxygen. Overall, ExoScreen technique could be a versatile approach for biomarker screening in various diseases (Shao et al., 2018). As a proof-of-concept, ExoScreen technique is applied for detecting colorectal cancer EVs biomarkers and to distinguish between healthy donors and colorectal cancer patients (Yoshioka et al., 2014).

2.1 | Cell-derived vesicles in targeted imaging and cancer therapeutic applications

Cell-derived extracellular vesicles exhibit good biocompatibility, diagnostics, and cancer therapeutic applicability due to inherently available proteins and surface biomarkers (Latifkar et al., 2019; Salunkhe et al., 2020; Shao et al., 2018; Tran et al., 2020; Y. Wang et al., 2019). Naturally available surface biomarkers and unilamellar lipid bilayer membrane in cell-derived vesicles improve their stability in the bloodstream (J. Wang, Chen, & Ho, 2021; Y. Wang et al., 2019). These nanosized structures have been applied for tissue regeneration, targeted cancer cell imaging, stimuli active therapeutics, and drug delivery applications (Chiang et al., 2021; Qambrani et al., 2021; Toh et al., 2018; J. Wang, Chen, & Ho, 2021; Yi et al., 2021). The available large cavity of vesicles makes them suitable for carrying excess amount of anticancer drug molecules or other therapeutic agents to the specific target site (Qambrani et al., 2021; J. Wang, Chen, & Ho, 2021). The significant importance and outcomes of these cell-derived particles have been achieved at preclinical rodent models (Cho et al., 2017; Qambrani et al., 2021; Shahir et al., 2020; J. Wang, Chen, & Ho, 2021). So far, various surface engineered vesicles have been documented in the literature showing their suitability for drug and gene delivery, imaging, and cancer therapies (Chiang et al., 2021; Cho et al., 2017; Qambrani et al., 2021; Toh et al., 2018; J. Wang, Chen, & Ho, 2021; Yi et al., 2021). Small size (30–100 nm in size) spherical soft vesicles are sufficient enough to diffuse into the solid tumor microenvironment via enhanced permeability and retention (EPR) effect followed by passive targeting approach (Chiang et al., 2021; Cho et al., 2017; Y. Liu et al., 2019; Qambrani et al., 2021; Shao et al., 2018; Yi et al., 2021). Further, to improve the targeting delivery efficacy into solid tumors, nanovesicles are typically engineered with targeted small biomolecules like peptides, folic acid, antibodies, and so forth. Conversely, the presence of attached targeting ligands on the surface of the vesicle may have an undesirable impact on targeted delivery because of the boosted immune elimination. Furthermore, the targeting ability of these targeting ligands functionalized vesicles is not specific for a wide range of cancer cells because of different receptors from versatile genetic or phenotypic heterogenic tumor cells.

Additionally, these vesicles have better biocompatibility, stability, and circulation over synthetic soft vehicles like liposomes (Chiang et al., 2021; Cho et al., 2017; Y. Liu et al., 2019; Prasad et al., 2018). However, low product yield, poor reproducibility, heterogeneous particle distribution, and low targeting specificity toward cancer cells limit their further in vivo and clinical applications (Shao et al., 2018). Moreover, these vesicle structures have been engineered with various targeting ligands or surface modifiers to improve their targeting applicability. Overall, no significant outcomes have been achieved for these cell-derived vesicles for cancer therapeutics and still facing various critical hurdles like specific targeting, stability, bio-distribution, circulation, and so forth (Y. Liu et al., 2019; Shao et al., 2018). Apart from this, such vesicles are secreted (~6 to 12 μg per 10^6 for 7 days) from various cell types during in vitro culture, and also present in the cell culture media and in in vivo body fluids (H. Qi et al., 2016; Shao et al., 2018). Notably, blood is a better source of soft nanovesicles production as compared to other in vitro sources. Reticulocytes in the bloodstream release about 10^{14} (at least 200 μg) vesicles/or exosomes per day during their maturation into erythrocytes that contains transferrin (Tf) membrane proteins (H. Qi et al., 2016).

For localized imaging and early-stage diagnosis, molecular imaging is an effective approach over the conventional imaging modalities as molecular imaging provides precise examination of the targeted site based on molecular differences and not just based on anatomical changes (Zhong et al., 2019). So far, imaging modalities like Positron Emission Tomography (PET), X-ray Computed Tomography (X-ray CT), Magnetic Resonance Imaging (MRI), Photoacoustic Imaging (PAI), and so forth have been proposed for targeted tumor imaging using surface engineered exosome-based nanocontrast agents as shown in Figure 3a–h (Betzer et al., 2017; Ding et al., 2018; Jung et al., 2020; Liang et al., 2022; T. Liu, Zhu, et al., 2020; H. Qi et al., 2016; Zhong et al., 2019). Among these imaging approaches, x-ray CT and MRI

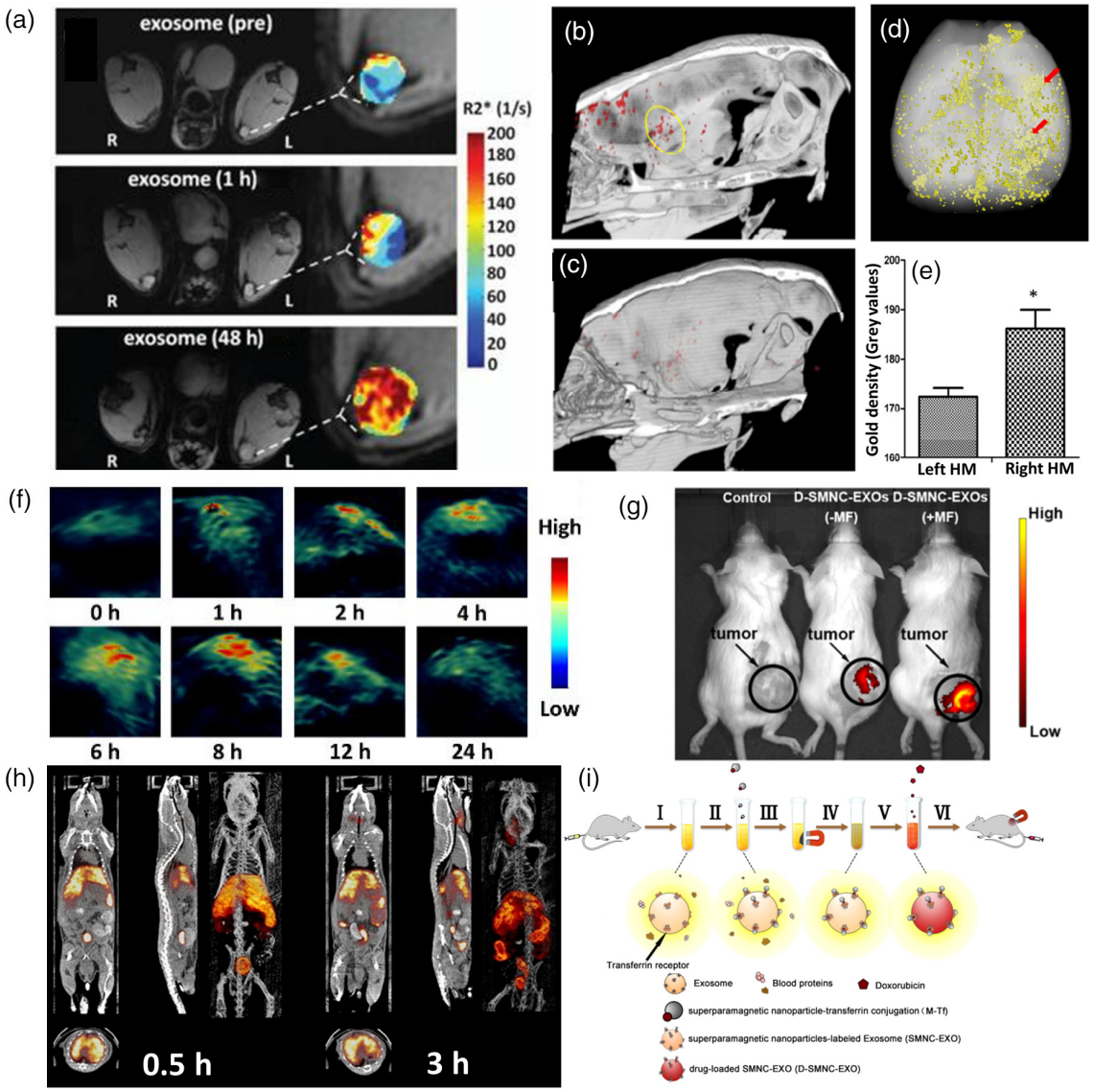

FIGURE 3 (a) Iron oxide nanoparticle encapsulated exosomes as MRI imaging agents for in vivo imaging, T1-weighted images, and R2* mapping after 48 h injection showing exosomal nanocontrast agents accumulation in lymph node, (b–e) gold nanoparticles decorated exosomes as radiocontrast agents for x-ray CT imaging of mice with acute striatal stroke, (b) after 24 h postadministration, yellow circle indicates the ischemic region, (c) in vivo CT image of control animal (saline injection), (d) ex vivo CT imaging of brain with gold quantification after 24 h post injection, (e) gold density analysis from CT images *($p < 0.05$), (f) RGD attached V_2C-TAT decorated exosomes as PA imaging agents for in vivo PA images at various time points of postinjection with signal intensities of mice, (g) NIRF imaging of tumor bearing mice using emissive exosomal based nanocontrast agents, (h) ^{99m}Tc-HMPAO functionalized exosomes as imaging agents for single-photon emission computed tomography/computed tomography (SPECT/CT) imaging at in vivo level at various time of postinjection and (i) schematic showing the fabrication and targeted delivery of engineered exosomes; (I) fresh serum collection from healthy mice, (II) predialyzed serum incubation with M-Tfs, (III) magnetic separation and purification of designed exosomes, (IV) dispersion of engineered exosomes, (V) drug loaded exosomes, and (VI) intravenous injection of drug loaded exosomes into tumor-bearing mice. Reproduced with permission from American Chemical Society, MDPI, and Wiley (Barjesteh et al., 2021; Betzer et al., 2020; Y. Cao et al., 2019; H. Qi et al., 2016)

imaging modalities are most attractive diagnostic approaches due to better imaging resolution and noninvasive nature of these techniques. Whereas Positron Emission Tomography (PET) is limited due to the short lifetime and sensitivity of the radioactive tracers (Barjesteh et al., 2021; H. Qi et al., 2016). Apart from these imaging modalities, Photoacoustic Imaging (PAI) is also recently developed clinically relevant imaging modality which is based on the concept of photo-acoustic effect and integrated ultrasound imaging where imaging agent in the biological sample absorbs the pulsed laser

radiation and turn them into an acoustic signal (Barjesteh et al., 2021; Ding et al., 2018; Liang et al., 2022). Notably, PAI has deep penetration, high spatial resolution, and noninvasive imaging ability.

Cell-derived exosomes and nanoparticulate engineered exosomes have been applied for localized multimode tumor imaging due to their good biocompatibility, better circulation, and easy accumulation in a solid tumor environment without any side effects as shown in Figure 3 and Table 2 (Barjesteh et al., 2021; Y. Cao et al., 2019; H. Qi et al., 2016). Exosomes encapsulated iron oxide nanoparticles have been used as an MRI imaging agent for lymph node imaging (Figure 3a). Similarly, exosomes have been engineered with many other imaging probes such as ^{99m}Tc-HMPAO, V_2C-TAT@Exosomes attached RGD, Ag_2Se@Mn QD-labeled exosomes, and so forth for various imaging modalities such as x-ray CT, PAI, Near Infrared (NIRF) Imaging, Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT), and so forth as shown in Figure 3b–h. On the other hand, exosomes have also been fabricated and applied for cancer therapeutics and targeted delivery applications (Figure 3i). It should be noted that exosomes are facing various challenges for clinical translational therapy (Betzer et al., 2020; H. Qi et al., 2016). So far, various nanosized synthetic hybrid materials based on organic and inorganic components have been applied for therapeutic applications (Conde et al., 2016; Prasad et al., 2020; Wong et al., 2020). However, these systems are limited for further translational and therapeutic applications due to their low biocompatibility, nonspecific biodistribution, and long-term toxicity effect (Conde et al., 2016; Prasad et al., 2020). Therefore, cell-derived vesicles "exosomes" based therapeutic platforms resolve the above-addressed critical hurdles. Because of good biocompatibility, dye-tagged exosomes have been tested for solid tumor imaging and their bio-distribution followed by using intratumoral injection as shown in Figure 4a,b.

Of late, surface-engineered exosomes have been documented for different therapeutic applications such as chemotherapy (because of drug delivery ability), light-mediated photothermal and photodynamic therapy, immunotherapy, and so forth (Toh et al., 2018). In the exosomes, their two-layer membranes play an important role in protecting loaded cargo/therapeutic molecules from the external environment because of the presence of natural protector and an ideal capsule layer (Shahir et al., 2020; Sharma et al., 2021). For example, it has been noticed that the drug-loaded exosomes show significantly reduced toxicity and negative effect of anticancer drug doxorubicin on the heart when they are applied for chemotherapeutic applications (Sharma et al., 2021). In other example, curcumin-loaded exosomes have shown reduced lung inflammation and higher survival of the mice as compared to the curcumin treatment only (Conde et al., 2016). Furthermore, in the case of paclitaxel-loaded exosomes (Sun et al., 2010) decorated with aminoethyl anisamide-polyethylene glycol, the drug uptake, and penetration depth have been noticed in the lung tumor as compared to other major organs. Specifically, exosomes obtained from LIM1215 cells that are engineered with doxorubicin and superparamagnetic iron oxide nanoparticles, and A33 antibodies as target agents demonstrated reduced drug cytotoxicity in the heart and increased drug effect on the colon cancer cells along with photodynamic therapeutic response (Sun et al., 2010). Human MSCs cell derived exosomes engineered with Taxol showed higher lung cancer (A549), ovarian cancer (SK-OV-3), and breast cancer (MDA-hyb1) cell death with reduced metastatic activity around 50% in the major organs (Melzer et al., 2019; Salarpour et al., 2019; Sun et al., 2010). Lately, these exosomal nanotherapeutic systems have been tested for in vivo examinations and have been noticed as an ideal therapeutic agents for solid tumor reduction, specific bio-distribution, bio-safety, and bio-compatibility, immunogenic activities, crossing biological barriers, and so forth (Melzer et al., 2019, 2020; Salarpour et al., 2019).

Importantly, cell-derived exosomes have specific surface composition and biomarkers along with their endogenous origin, hence, they have long circulation and more biocompatibility as compared to lipid self-assembled liposomes (Pick et al., 2018). The importance of exosome over liposomes has been evaluated through tumor imaging and antitumor activity studies as shown in Figure 4. In these studies, dye-tagged exosomes and liposomes have been injected on the tumor site to examine the tumor imaging and specific biodistribution at a different time of postinjection (1 and 24 h, see Figure 4a,b). Engineered exosome is depicted in Figure 4c. Further, incorporating targeting peptides or proteins on the surface of exosomes stimulate their biological performance for targeted therapeutic efficacy (Pick et al., 2018). However, precise targeting in the deep tissues of the human body is very difficult and receptor saturation is another critical hurdle for specific targeting (Melzer et al., 2019, 2020; Pick et al., 2018; Salarpour et al., 2019). Moreover, exosome-based theranostic platforms are far from addressing the inherent or natural targeting ability for cancer cells or tumors that limit their applicability for cell-based or biological anticancer therapy (Pick et al., 2018). It has been noticed that external stimuli receptiveness improves the delivery of therapeutic agents into the target tumor site (Do Cong Thang et al., 2019). The effective and stimuli responsiveness of these engineered systems improve their specific accumulation at tumor sites and enhance the on-site drug release with reduced side effects (Thang et al., 2019; Illes et al., 2017; B. Yang et al., 2019).

TABLE 2 Bioinspired soft nanovesicles and their cancer therapeutic application

S. no.	Bioinspired nanovesicles	Encapsulated probes/ agents	Encapsulation method	Size (nm)	Advantages	Application	References
1.	Liposomes	Doxorubicin	Thin film hydration	158–165	Safe and biocompatible	Drug delivery	(Lakkadwala & Singh, 2019)
2.	Liposomes	Doxorubicin, daunorubicin, vincristine sulfate, paclitaxel, irinotecan	–	–	Biocompatible	Cancer chemotherapy	(Panahi et al., 2017; Pattni et al., 2015)
3.	Liposomes	Indocyanine green (ICG) dye	Thin film hydration	130	Clinically translatable system	Imaging	(Wood et al., 2021)
4	Mesenchymal stem cells (MSCs) exosomes	1. Gold nanoparticles 2. miR-146b 3. siRNA	Treating Parent cell, EGFR targeting in glioma in rats	~130	Biocompatible, Fluorescent, easy accumulation, long time retention on target site	Imaging, drug/gene delivery	(Barjesteh et al., 2021; Betzer et al., 2020; Kalluri & LeBleu, 2020)
5.	Human umbilical cord mesenchymal stromal cells (HUC-MSCs) exosomes	Gadolinium ion	–	~170	Targeted imaging	Imaging	(Abello et al., 2019)
6.	Monocyte cell membrane-derived nanoghosts	Doxorubicin	–	~200		Drug delivery	(Krishnamurthy et al., 2016)
7.	Extracellular vesicles	Nucleic acids	–	120	–	Nucleic acids delivery	(Tamura et al., 2021)
8.	Blood serum	IrO_2 and Fe_3O_4	In situ biosynthesis	NA	Safe, stable, long luminescence, paramagnetic	Imaging	(Barjesteh et al., 2021)
9.	Murine melanoma cells (B16-F10)	SPIONs	Electroporation	~100	Biocompatible, safe, potential MRI agent	Imaging	(Betzer et al., 2020)
10.	Human embryonic kidney (HEK293T)	Gold nanoparticles	Genetically modified cells	~100–105	Low specificity, large surface area, optical responsive	Imaging	(Barjesteh et al., 2021)
11.	Gastric cancer (SGC7901)	Gold-Iron nanoparticles	Treating parent cells	~115	Paramagnetic, biocompatible, fluorescent	Imaging	(Betzer et al., 2020; H. Qi et al., 2016)

TABLE 2 (Continued)

S. no.	Bioinspired nanovesicles	Encapsulated probes/ agents	Encapsulation method	Size (nm)	Advantages	Application	References
12.	Cancer cells (4T1, PC3, MCF-7)	^{111}In-oxine	Direct-incubation	~100	Radiodensee, safe, stable	Imaging	(H. Qi et al., 2016)
13.	Triple-negative breast cancer cells	SPION	Indirect	NA	NA	Imaging	(Betzer et al., 2020)
14.	Red blood cells vesicles	1. Graphene quantum dot nanozyme 2. Camptothecin 3. Red blood cell membrane-camouflaged nanoparticles	Incorporated during nanozyme preparation	~150	Targeted cancer therapy, biocompatible	Drug delivery, Imaging	(Malhotra et al., 2019; H. Qi et al., 2016; Xia et al., 2019)
15.	Mesenchymal stem cells	Gold nanoparticles	Direct-incubation	~80–100	Biocompatible, high radiodensity, stable, long circulation	Imaging	(Barjesteh et al., 2021)
16.	Erythrocyte vesicles	1. ^{99m}TC-tricarbonyl 2. Erythrocyte membrane-coated upconversion nanoparticles	Direct-incubation	110	Biocompatible	Imaging, drug delivery, cancer therapy	(Betzer et al., 2020; X. Han et al., 2019; H. Qi et al., 2016; Rao et al., 2017)

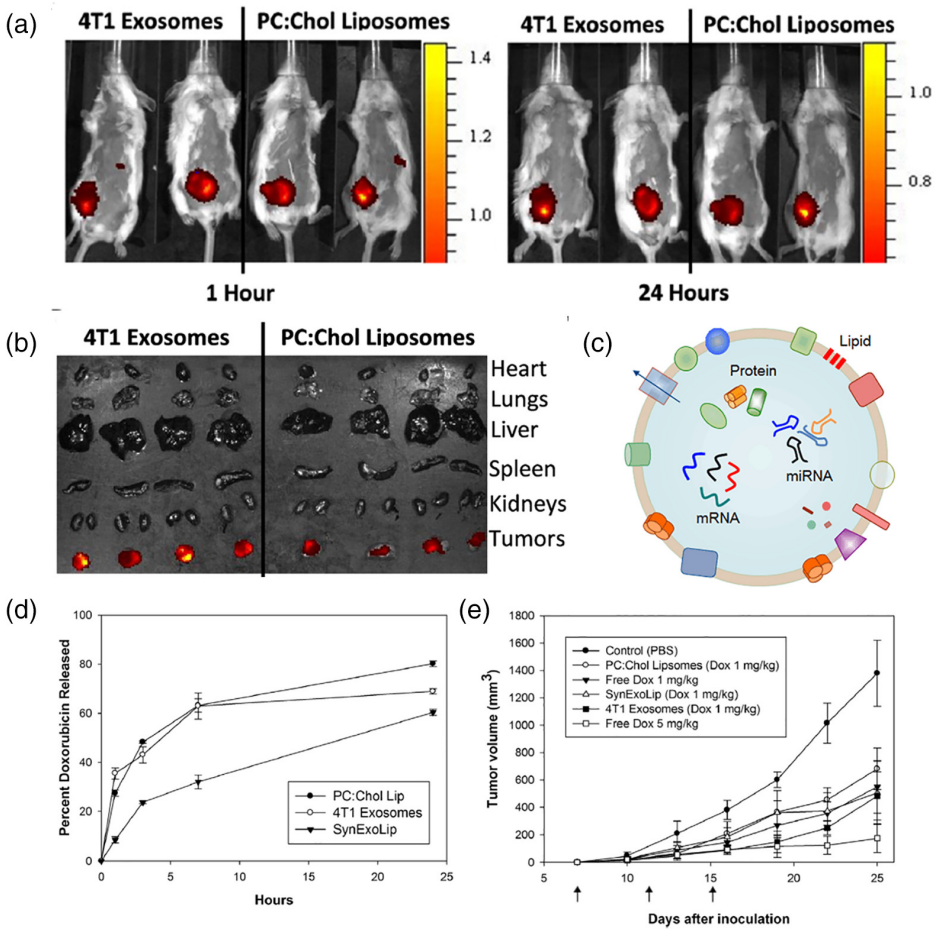

FIGURE 4 (a) Time-dependent near-infrared imaging of 4T1 tumor-bearing in vivo models using dye tagged exosomes and liposomal (PC:Chol liposomes) systems using intratumoral injection (60 μg 4T1 exosomes or PC:Chol liposomes dose), (b) ex vivo near-infrared imaging of major organs and tumors after 24 h passage of time, (c) diagram of exosome taken from Google images, (d) time-dependent drug doxorubicin release kinetics of exosomes, PC:Chol liposomes and SynExoLiposomes, and (e) the tumor growth reduction analysis using exosome and liposomal hybrids as therapeutic agents, for the treatment drug conjugated exosome and liposomes were injected on 7th, 11th, and 15th days. Reproduced with permission from Smyth et al. (2015), Elsevier

2.2 | Major advantages and challenges of cell-derived vesicles over liposomes

Cell-derived vesicles have been recognized as natural signaling vehicles that play an important role in intercellular communication and as carrier platforms for small molecules from one cell to other cells (Becker et al., 2016). For example, exosomes play a major role in cellular communication through the transport of their entrapped biomacromolecules from the host cell to a recipient cell. Due to large cargo loading capacity and biological nature, exosomes have been used to carry multiple drug/or cargo molecules to the cancer cells/tumors for anticancer therapeutics efficacy shown in Figure 4d,e (Becker et al., 2016; Juan & Furthauer, 2018; Margolis & Sadovsky, 2019; Paolicelli et al., 2019; Pucci et al., 2016). However, the immune response of exosomes in the cancer treatment is unclear (Tamura et al., 2021) though they are well documented for targeted cancer therapy (J. Wang, Dong, et al., 2018) and nucleic acids (DNA and RNA) delivery to the targeted cells as compared to other carrier systems (Becker et al., 2016; de la Torre Gomez et al., 2018; Gyorgy et al., 2011; H Rashed et al., 2017; Y. Han, Jia, et al., 2018; Juan & Furthauer, 2018; M. Li et al., 2014; Margolis & Sadovsky, 2019; Paolicelli et al., 2019; Pucci et al., 2016; Pullan et al., 2019; Shao et al., 2018; Skog et al., 2008; Tamura et al., 2021). Moreover, these nanosized cell-derived vesicle structures can affect genetic changes in various cells which are suitable platforms to manipulate gene expression in gene therapy. On the other hand, various drug molecules especially, anticancer drugs are unstable during in vivo therapeutic conditions and these drugs face serious challenges such as chemical toxicity, nonspecific distribution, blood disorders, drug resistance, low specificity to the target site, and so forth (Hurria et al., 2011).

To overcome the above highlighted major challenges, various nanosized hybrid systems like organic, inorganic, bio-inorganic, and so forth have been proposed, but, their chemical toxicity is always a major obstacle (Jain et al., 2020; Prasad et al., 2016; Y. Zhang et al., 2016). Importantly, exosomes can resolve these critical issues due to their good biocompatibility, small size (between 30 and 150 nm), biological nature, high cargo capacity, and better stability as compared to chemically synthesized nanohybrids systems (Ni et al., 2020; Shao et al., 2018). Second, lipid self-assembled liposomal hybrids also could resolve these challenges due to their controlled particle size, high cargo capacity, and good biocompatibility (Lakkadwala & Singh, 2019). Moreover, liposomal systems have been recognized as the most preferred drug delivery systems for improving therapeutic intervention (Figure 4e; Al-Ahmady & Kostarelos, 2016; Fan et al., 2021; Lakkadwala & Singh, 2019; Panahi et al., 2017). So far, various liposomal hybrid systems have been proposed for clinical trials, and few of them have even been approved for clinical applications (Sato et al., 2016; Smyth et al., 2015). However, liposome-based delivery systems are not compatible due to their inability to avoid the host immune system (Panahi et al., 2017; Smyth et al., 2015). Furthermore, liposomes also face critical concerns of low biological nature, chemical toxicity, rapid protein corona layers on their surface, nonspecific targeting and distribution, and macrophage uptake during their in vivo applications.

In the case of exosomes, intrinsically available surface biomolecules prevent protein corona formation on their surface during blood circulation and macrophage phagocytosis. Furthermore, the surface biomarkers on exosomes improve long circulation half-life, capability to deliver naturally entrapped therapeutic nucleic acids (mRNA and siRNA) to the cytoplasm and the nucleus of site-specific cancer cells, and enhance cellular uptake in drug resistance cancer cells (Barjesteh et al., 2021; Betzer et al., 2017; Y. Cao et al., 2019; Ding et al., 2018; Liang et al., 2022; T. Liu, Zhu, et al., 2020). Also, exosomes as drug delivery vehicles avoid accumulation in the liver that helps to evade the first pass metabolic effect before reaching the target sites (Conde et al., 2016; Melzer et al., 2020). Whereas, liposomal-based therapeutic systems are far from achieving these advantages. Overall, exosomes have various advantages over liposomal hybrid systems (Smyth et al., 2015), especially for tumor imaging and growth inhibition of tumor. However, despite huge popularity of exosomes, localized diagnosis and treatment of exosomes for cancers are still not well explored and understood. The production of exosomes from cancer cells is complex and challenging. These cell products have high heterogeneity and different types of surface biomarkers even if they are obtained from one type of cells (Mathieu et al., 2021; Salunkhe et al., 2020). Further, exosomes still face major disadvantages such as low product and reproducibility, heterogeneity and low purity during their production, lack of natural targeting ability for the specific cancer cells/tumors, and so forth that limit their clinical trial applications (Shao et al., 2018). To overcome the critical limitations of cell-derived exosomes, the fused exosome–liposomal structure, artificial exosomes, or exosomes-stimulated liposomes could be considered as more suitable systems, but these systems could not resolve major safety problems (Sato et al., 2016).

3 | BIOINSPIRED MEMBRANE NANOVESICLES

Apart from cell-derived exosomes, plasma membrane-derived nanoparticles are another major class of natural vesicles which have various natural targeting molecules on their surface and large cavity for drug payload (Fang et al., 2017; Yuan et al., 2021; Figure 5). These membrane nanovesicles are prepared through biological process whereas, exosomes are naturally released from various cells during their culture as shown in Figure 5a (Fang et al., 2017; Ni et al., 2020; Sato et al., 2016; Smyth et al., 2015; Yuan et al., 2021; Y. Zhang et al., 2016). Naturally available surface biomarkers/or proteins on cell membrane-derived vesicles make them more suitable for targeted drug delivery and cancer therapeutic applications (Z. Chen et al., 2019; Yuan et al., 2021) as highlighted in Table 3. As of now, site-selective delivery of cargo molecules (imaging or therapeutic agents) on the desired site is being questioned (Y. Zhang et al., 2016). The ultimate goal of bioinspired nanovesicles is to achieve a significant therapeutic effect and accumulation on the specific site of disease with diminishing off-targeting effects (Yuan et al., 2021). Bioinspired nanovesicles are progressively being recognized as intercellular mediators for the delivery of effective molecules like drugs/growth factors or externally loaded nucleic acid (Z. Chen et al., 2019). Remarkably, certain types of biological nanovesicles have shown their image-guided anticancer therapeutic responses and tissue regeneration applications due to their unique physiochemical characteristics (Z. Chen et al., 2019; Fang et al., 2017; Ni et al., 2020; Sato et al., 2016; Smyth et al., 2015; Yuan et al., 2021; Y. Zhang et al., 2016).

Red blood cells (RBCs) derived nanoerythrosomes (X. Han, Wang, & Liu, 2018, Han et al., 2019; Javed et al., 2021) have been proposed for targeted drug delivery applications. Moreover, these nanosized ghost platforms have been

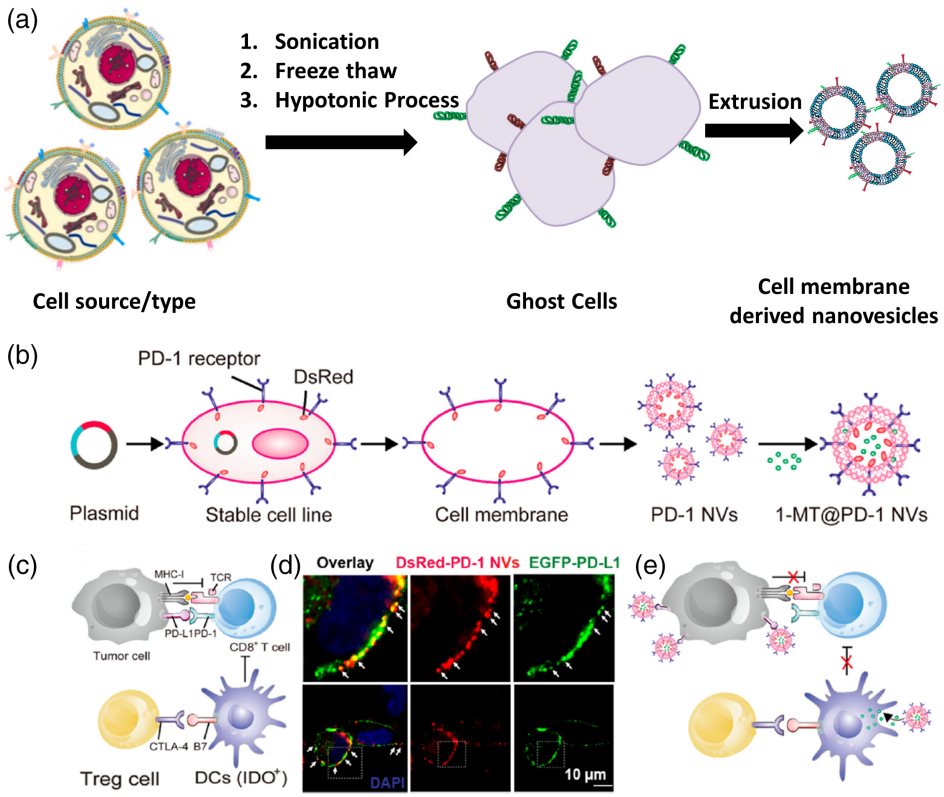

FIGURE 5 (a) Schematic showing the preparation of cell membrane-derived nanovesicles and (b) fashioning genetically engineered cells into nanovesicles with PD-1 receptor decorating on the surface and 1-MT loading in the large cavity, PD-1 is tagged with DsRed protein, (c) CD8+ T-cell activity suppression via PD-1 and IDO pathways, (d) microscopy images of co-localization of PD-1 nanovesicles and PD-L1 (green) on B16F10 melanoma cell membrane, and (e) biomimetic nanovesicles for synergistic deterioration of CD8+ T cells by blocking dual tolerance pathways. Reproduced from American Chemical Society and Elsevier (Z. Chen et al., 2019; Mohr & Zwacka, 2018) and Google image with permission

applied for targeted imaging and photothermal therapy of cancer (Ye et al., 2019). Compared to RBCs, stem cells have been recognized as a versatile source for cell membrane-based nanovesicles/or ghosts platform due to their tumor targeting specific surface biomarkers (Mohr & Zwacka, 2018; Wu et al., 2019). Importantly, mesenchymal stem cell-derived nanostructures have shown their therapeutic performance in preclinical models (Mohr & Zwacka, 2018). Apart from stem cells, White Blood Cells (WBCs) derived nanodelivery vesicles are in the current trend, which have unique functions for biomedical applications (Hou et al., 2018). As compared to chemically designed biomaterials including liposomes, these bioinspired nanovesicles demonstrate better properties such as high biocompatibility, easy and smooth circulation, site-selective targeting, long time circulation, easily biodegradable, better biosafety, nonimmunogenicity, and so forth which make them more suitable for targeted imaging and therapeutic applications (Smyth et al., 2015; Wu et al., 2019). In addition, these biological systems have the potential ability to escape from clearance by the host immune system and pass through physiological barriers due to their specific surface biomarkers and small particle size (Z. Chen et al., 2019; X. Han, Wang, & Liu, 2018, Han et al., 2019; Javed et al., 2021; Mohr & Zwacka, 2018; Wu et al., 2019; Ye et al., 2019). In fact, animal models and the human body possesses a highly active and specialized immune system which is dynamic for protecting the body from harmful pathogens, foreign administered materials, and identification of abnormalities within cells or tissues.

In the literature, the bioinspired and genetically engineered nanovesicles obtained from various cell sources (normal cells, blood cells, stem cells, immune cells, cancer cells, and so forth) have been documented for targeted antitumor activities and cancer vaccines as shown in Figure 5b–d (Z. Chen et al., 2019; X. Han, Wang, & Liu, 2018, Han et al., 2019; Javed et al., 2021; Mohr & Zwacka, 2018; Wu et al., 2019; Ye et al., 2019). Further, these systems have been studied for localized delivery of various therapeutic molecules and chemotherapeutic drugs with their promising effects to kill cancer cells selectively (Z. Chen et al., 2019). Moreover, these bioinspired nanosized vesicles demonstrate specific organotropic behavior in cell-to-cell communication (K. Lee et al., 2018). At the cellular level, the surface markers of

TABLE 3 Advantages and disadvantages of cell membrane-derived nanovesicles

Cell source	Advantages	Disadvantages	References
Cancer cell membrane	1. Avoid the immune response 2. Possess tumor-specific antigen 3. Homotypic tumor targeting 4. Generate tumor-specific immune response 5. Long circulation 6. Better biocompatibility 7. As an active anticancer vaccine	1. Complicated purification process 2. Low yield	(Betzer et al., 2020; Z. Chen et al., 2019; Mohr & Zwacka, 2018; H. Qi et al., 2016)
Platelet membrane	1. Better platforms for homeostasis therapy 2. Good biocompatibility for the immune system and response 3. Evading immune response 4. Specificity for tumor targeting and drug delivery 5. Long circulation	1. Complicated synthetic and purification protocol 2. Low immunogenic potential 3. Low product yield	(Z. Chen et al., 2019; Le et al., 2021)
Red blood cells (RBCs)	1. Avoid the immune response 2. Long blood circulation 3. Easy surface functionalization 4. Generate tumor-specific immune response 5. Site-selective tumor targeting and drug delivery applications	1. Complicated synthetic and purification protocol 2. Low immunogenic potential 3. Time taking process for controlled particle size preparation and purification	(Z. Chen et al., 2019; X. Han, Wang, & Liu, 2018, Han et al., 2019; Javed et al., 2021; Malhotra et al., 2019; H. Qi et al., 2016; Rao et al., 2017; Xia et al., 2019; Ye et al., 2019)
White blood cells (WBCs)	1. Evade the immune response 2. Long blood circulation 3. Tumor-specific targeting ability 4. Regulation of inflammatory response 5. Disease areas specific targeting and binding ability 6. Better biocompatibility 7. Better stability in biological environment	1. Complexity of WBC membrane 2. Low yield and complicated purification process	(Z. Chen et al., 2019; Hussain et al., 2021; Le et al., 2021)
Mesenchymal stem cells (MSCs)	1. Avoid the immune response 2. Long blood circulation 3. High pay load 4. Better safety, biocompatibility, and stability in biological environment 5. Natural targeting 6. Tumor or cells specific binding ability 7. Evade the immune response	Complex preparation methods	(Abello et al., 2019; Barjesteh et al., 2021; Z. Chen et al., 2019; Gimona et al., 2021; Gowen et al., 2020; Kalluri & LeBleu, 2020; W. Lin et al., 2019; Mohr & Zwacka, 2018; Wu et al., 2019)

these biological systems are capable of communicating with the immune system through bio interface characteristics where surface biomolecules are in direct contact with its surrounding biological environment (Figure 5d,e; Mohr & Zwacka, 2018; Wu et al., 2019). The natural content of available lipid bilayers in these bioinspired nanovesicles membranes protects the premature release of their loaded cargos and their degradation during blood circulation (Mohr & Zwacka, 2018). Importantly, this whole process is predominantly critical during blood circulation where these bioinspired nanovesicles first interact with immune cell and protein molecules to form surface corona and then various successive interactions happen directly or indirectly that regulate the reaction of immune cells with bioinspired nanovesicles in the bloodstream (Z. Chen et al., 2019; Mohr & Zwacka, 2018). Therefore, the overall composition and

surface biomarkers of these bioinspired nanovesicles significantly control the ability to overcome the biological barriers modeled by the immune system (Hou et al., 2018; Hussain et al., 2021; Mohr & Zwacka, 2018; Wu et al., 2019).

In recent years, cell membrane-based nanoplatforms/or bioinspired nanovesicles have seen a growing interest in the field of naturally targeted imaging, drug delivery, and cancer therapies (Z. Chen et al., 2019; X. Han, Wang, & Liu, 2018, Han et al., 2019; Hou et al., 2018; Hussain et al., 2021; Javed et al., 2021; Mohr & Zwacka, 2018; Wu et al., 2019; Ye et al., 2019). So far, various biomimetic technologies have been developed to prepare cell membrane-based bioinspired nanovesicles (Z. Chen et al., 2019). To mimic the biological characteristics, these bioinspired nanovesicles are formulated from the whole cells, ghost cells, and the integrated cell-derived membrane proteins that allow them to escape immune clearance and increase their natural or inherent targeting ability (Figure 5c–e; Z. Chen et al., 2019; X. Han, Wang, & Liu, 2018, Han et al., 2019; Hou et al., 2018; Hussain et al., 2021; Javed et al., 2021; Mohr & Zwacka, 2018; Wu et al., 2019; Ye et al., 2019). Furthermore, these platforms have demonstrated their biomimicry potential to overcome the biological barriers posed by the immune system (Hussain et al., 2021). On the other hand, bioinspired nanovesicles empower cells communication to modulate the immune response (Hussain et al., 2021). Biologically prepared nanovesicles have major advantages because of their inherent performance in a biological environment for targeted delivery or immune modulation. Liposomes and exosomes are incapable to demonstrate these features, especially for cancer therapeutic applications (Z. Chen et al., 2019; Mohr & Zwacka, 2018).

3.1 | Membrane nanovesicles in targeted imaging and cancer therapeutic applications

Membrane nanovesicles have better strength compared to the liposomes and exosomes in terms of circulation, stability, easy penetration of vascular tissues, and target sites of cancer cells/tumors, low immunogenicity, and natural/or inherent targeting abilities as shown in Figure 6 (Hou et al., 2018; Hussain et al., 2021; Mohr & Zwacka, 2018; Wu et al., 2019). Certain types of cell membrane-derived nanosized vesicles hold unique characteristics like long circulation, site-selective targeting, stability, evade the immune response or reduced immunogenicity, tumor homing, and so forth which make them suitable for cancer imaging and therapy applications (Wu et al., 2019). Importantly, cell-derived nanovesicle components improve the protection for the inner parts, and the surface biomarkers or proteins of these nanovesicles evade immunological recognition by immune cells during their blood circulation (Mohr & Zwacka, 2018; Wu et al., 2019). Moreover, biocompatibility of membrane ingredients is the key parameter of these bioinspired vesicles that make them clinically relevant platforms (Z. Chen et al., 2019; Mohr & Zwacka, 2018).

Lately, mesenchymal stem cells (MSCs) based nanosized vesicles have gained a great attention in cancer therapeutic applications (Gowen et al., 2020). These cells are overexpressed with various surface markers like CD90, CD105, CD73, and are defined as nonhematopoietic cells isolated from bone marrow (Gimona et al., 2021). Natural targeting has improved the imaging and therapeutic ability of these biomimetic/or bioinspired platforms. A natural tumor tropism benefits the active tumor-targeting ability of these stem cell-derived nanovesicles (Gimona et al., 2021). Furthermore, these vesicles are not affected by the high interstitial pressure and stiff extracellular matrix in the solid tumor and they can easily penetrate the deep tumor environment (Gimona et al., 2021; Gowen et al., 2020; W. Lin et al., 2019). In particular, these systems have demonstrated their biomimicry by communicating or transferring the biological features of native cells like platelets, red blood cells (RBCs), leukocytes, and so forth. For example, terminal Neu5Gc (NGpos) or terminal NeuAc (NGneg) engineered erythrocytes and cell nanoghosts (NGs) vesicles systems have been tested for antitumor activity as shown in Figure 6a–c.

More importantly, the molecular content of cell-derived nanovesicles "biological platforms" vary with respect to the source of cell types (W. Lin et al., 2019). Protein, glycans, and lipid contents of these biologics alter their natural targeting performance. For example, glycans expressed membrane nanovesicles have shown their targeting toward sialic acid-binding immunoglobulins (lectin receptors expressed on the HeLa cells) and CCR8-positive glioblastoma cells with specific biodistribution and good survival rate (Figure 6d,e; Fang et al., 2017; Gimona et al., 2021; W. Lin et al., 2019). Moreover, cancer cells derived vesicles and vesicles engulfed synthetic nanoparticles have been proposed as safe therapeutics platforms. These, designed platforms have been engineered with therapeutic molecules to suppress the cancer cells biomarkers. It has been observed that these biomimetic systems exhibit better antitumor activity in terms of significant tumor size and volume reduction with better survival rates in tested animals as shown in Figure 6f–j. However, it has been documented in the literature that the membranes derived nanovesicles cannot guarantee the availability of all the surface biomarkers such as proteins, antigens, and polysaccharides which are retained in the membrane of living cells (Fang et al., 2017; X. Gong et al., 2019; Q. Hu et al., 2017; Raza et al., 2021; Reuven et al., 2019; Zhan et al., 2020).

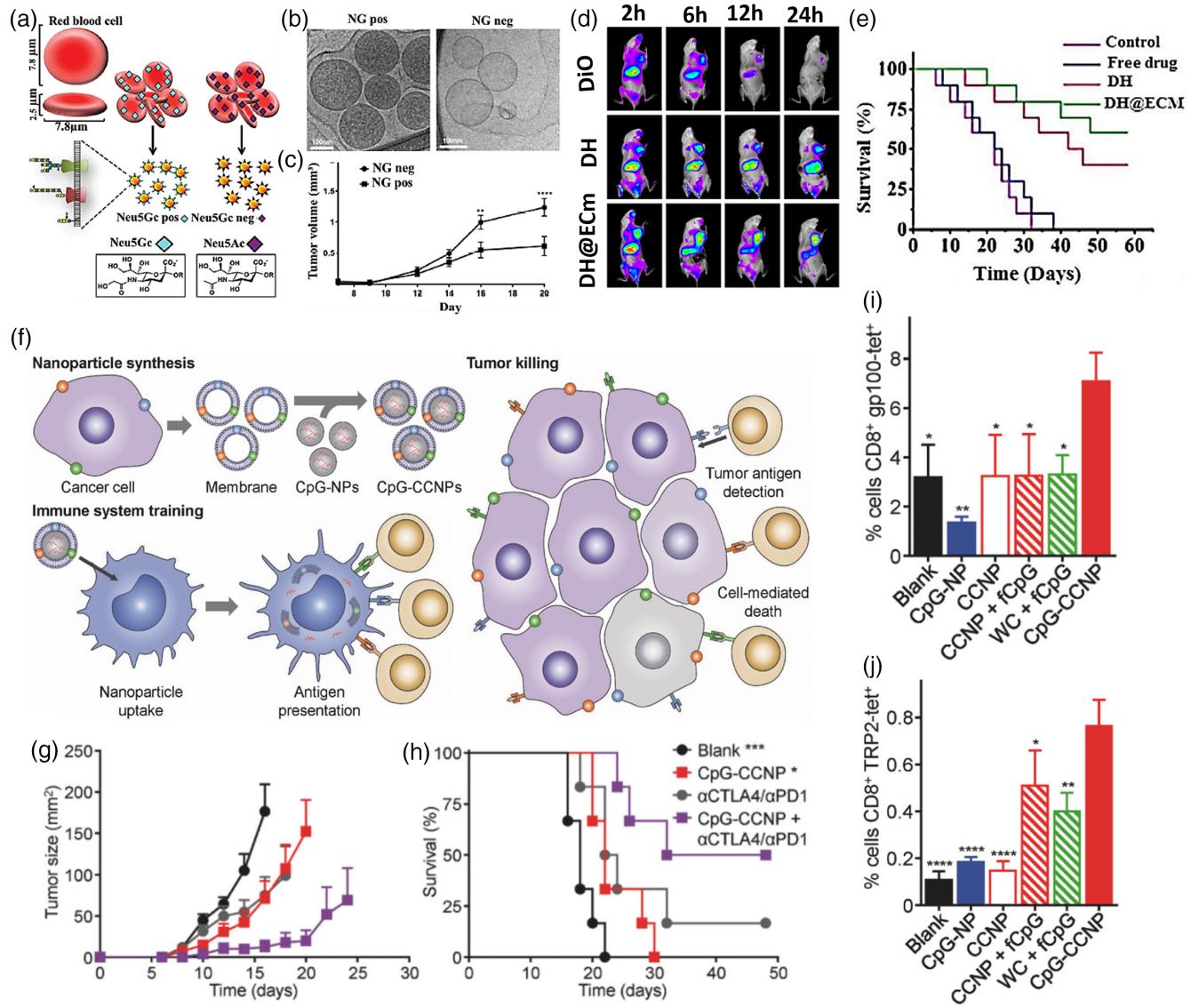

FIGURE 6 Various cell-derived nanovesicles for targeted imaging and therapeutics of cancer. (a) Schematic representation of erythrocytes and nanoghost (NG) decorated with terminal Neu5Gc (NGpos) or terminal NeuAc (NGneg) and (b) their transmission electron micrographs, (c) therapeutics ability for tumor volumes measurements showing growth inhibition of tumor, (d) bio-distribution of injected nanovesicles in tumor-bearing mice, (e) survival rate curve of different treatments of 4T1 tumor-bearing mice showing injected vesicles exhibit better compatibility, and (f–j) cancer cell membrane-based nanoparticles for multiantigenic anti-tumor vaccination with tumor size, survival rate curve, and tetramer staining analysis of T cells specific for gp 100 and TRP2. Reproduced with permission from Raza et al. (2021) and Reuven et al. (2019), Wiley and American Chemical Society

On the other hand, the application of nucleic acid therapy in the clinic needs safe and versatile delivery platforms. So far, viral and nonviral vectors have been proposed as the main approaches for nucleic acid therapy. Nevertheless, a number of safety concerns related to unwanted mutagenesis risks of induced immune responses and cancer have been documented which are associated with viral vectors. Therefore, significant efforts have been made to develop nonviral vectors formulations based on self-assembled biomolecules, lipid assemblies, bio-inorganic hybrids, polymeric carriers, and so forth.

Among them, cell-derived vesicles, namely, exosomes, membrane nanovesicles, plasma membranes, and so forth have been proposed as safe platforms for nucleic acid delivery applications (K. Wang, Kumar, et al., 2021). Importantly, delivery of nucleic acids (deoxyribonucleic acid, ribonucleic acid, messenger RNA, transfer RNA, ribosomal RNA, and RNA interference) or genes can reduce the communication of cellular protein that causes most diseases in humans. However, nucleic acid delivery suffers from various obstacles in human therapies due to the anionic nature and high

molecular weight of nucleic acids (J. Nguyen & Szoka, 2012; K. Wang, Kumar, et al., 2021). Further, the inability to penetrate deep into the tissues (solid tumors and brain) has been considered as another major limitation that results in poor therapeutic efficacy.

Significantly, the biological particles (exosomes, membrane nanovesicles, etc.) can fuse with the neighboring cells due to the presence of cellular markers on their surface. Henceforth, exosomes can cross several layers of tissues through the cell internalization process and assist as transport vehicles for mRNA, small RNAs (miRNA), and signaling factors delivery between cells. In addition, biological particles such as exosomes and plasma membrane based vesicles have specific surface proteins and lipids to specify their origin and destination apart from their biological cargo. These specific surface proteins make them suitable for early diagnosis of diseases and targeted therapeutics which are not achievable by polymersomes and liposomes. So far, various bioinspired vesicles based on exosomes and plasma membranes have been tested for nucleic acid therapy for solid tumors. For example, O'Brien used exosomes to deliver miRNA-134 (a tumor suppressant that reduces solid tumor of breast cancer) to Hs578Ts(i)8 triple-negative breast cancer cells where the cell migration and invasion are significantly reduced about 1.2-fold and anticancer activity is enhanced by about 2.1-fold (Pullan et al., 2019).

3.2 | Surface engineered nanovesicles and their targeting ability

Various nanosized platforms suffer from poor targeting ability, low biocompatibility, low blood circulation, poor stability, nonspecific distribution, and so forth (Ye et al., 2019). To improve these abilities, surface modifiers such as Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), folic acid, PEGylation, antibodies, peptides, and so forth have been decorated on the surface of nanosized platforms, namely, exosomes, membrane nanovesicles, plasma membranes, liposomes, and so forth (Jiang et al., 2021; Kang et al., 2020; Prasad et al., 2018, 2020). Especially, exosomes have been widely documented as a versatile platform for anticancer therapeutic applications, but, their clinical translation is slow and limited with the lack of specific delivery, high therapeutic doses requirement, and short half-life (<10 min; Jiang et al., 2021; Kang et al., 2020). Therefore, to overcome these encounters and develop exosomes as a promising delivery platform, exosomes have been modified with active targeting agents, namely, membrane anchor (BODIPY)-spacer (PEG)-targeting ligands (cyclic RGD peptide; ASL; Kang et al., 2020). Chemical conjugation and genetic transfection have been considered as promising approaches for surface modification of exosomes based systems.

It should be noted that active targeting strategy using biological ligands has been recognized as a promising approach to enhance the functional efficacy of exosomes to target cancerous cells. For example, ASL modified exosomes significantly overcome the challenges associated with premature release of loaded cargos, potential damage, and destabilizing of exterior surface of delivery system, inhibiting the degradation, and interactions of entrapped drugs from the extracellular environment. Moreover, ASL modification improves the circulation, targeting ability, and stability of exosomes in cancer mimicked environment where doxorubicin-loaded ASL-modified exosomes significantly reduce the growth of melanoma at in vitro and in vivo levels. Hence, surface-modified exosomes could be considered as a novel therapeutic system (Jiang et al., 2021; Kang et al., 2020).

On the other hand, TRAIL engineered exosomes demonstrate better tumor targeting, improved cellular uptake, and inhibit cell proliferation and migration. Further, this surface-modified system exhibit induced apoptosis of A375 cells through decorated TRAIL and inherent mitochondrial pathway at in vitro level (Jiang et al., 2021). Moreover, these TRAIL-modified exosomes demonstrate significant tumor reduction by suppressing tumor progression in the melanoma nude mouse model after intravenous injection. Overall, such surface-engineered exosome-based delivery systems provide an alternative solution for developing a potential approach for melanoma treatment with synergistic therapeutic and targeting efficacy (Jiang et al., 2021). Exosomes are similar to liposomal structures which have gained huge attention for targeted imaging, therapeutics, and drug delivery applications because of their inherent cell-homing ability and superior biocompatibility in comparison to synthetic nanoparticles.

4 | CLINIC IMPORTANCE AND TRANSLATION CHALLENGES

In the present time, exosomes, plasma membranes, and liposomes based systems have been considered as potential platforms for targeted therapy that highlight a major achievement in bio(nano)technology. These cell-based therapeutic agents demonstrate their specific preclinical/or clinical therapeutic advantages over conventional treatments due to

TABLE 4 Examples of bioinspired therapeutics and their approval (L. L. W. Wang, Janes, et al., 2021)

Name	Cell source	Approval usage	Year of approval/ trial number	Remarks
Strimvelis®	Autologous	Adenosine deaminase-severe combined immunodeficiency	2016	Genetically engineered
Provenge®	Dendritic cell, Autologous	Minimally symptomatic metastatic castrate-resistant prostate cancer	2010 by US FDA	Genetically engineered
Cartistem®	Allogeneic	Traumatic cartilage degeneration	2012 by KFDA	Genetically engineered
TEMCELL®HS Inj.	Allogeneic	Hematopoietic stem cell transplant	2015 in Japan	Genetically engineered
Holoclar®	Autologous	Limbal stem cell deficiency	2015	Genetically engineered
APCeden®	Autologous	Ovarian cancer, colorectal cancer, prostate cancer, lung carcinoma	2017	Genetically engineered
CreaVax-RCC®	Autologous	Metastatic renal cell carcinoma	2007	Genetically engineered
Sorrento Therapeutics for CAR T Cell	Autologous	Liver metastasis	NCT04037241 (Phase 2/3)	Genetically engineered
Celgene CAR T Cell	Autologous	Multiple myeloma	NCT03651128	Genetically engineered
CTX 110 (CRISPR Therapeutics)	Autologous	Lymphoma	NCT04035434 (Phase 1/2)	Genetically engineered
T Cells	Autologous	Leukemia, lymphoma	NCT03068416 (Phase 2)	Genetically engineered, third-generation CAR
Fred Hutchinson Cancer Center, T Cell	Autologous	Leukemia	NCT03326921	Genetically engineered
WT1-CTL (AtaraBiotherapeutics)	Autologous	Leukemia	NCT00620633	
E7 TCR T (National Cancer Institute)	Autologous	Oropharyngeal cancer	NCT04044950	Genetically engineered
City of Hope Medical Center, T Cell	Autologous	Glioblastoma	NCT02208362	Genetically engineered
JOINTSTEM® (NatureCell Co. Ltd.)	Autologous	Osteoarthritis	NCT03990805 (Phase 3)	

their dynamic response within the biological environment. Moreover, the cell-based platforms can restore impaired biological functions and augment the body's own ability to fight against disease (Ou et al., 2021). Various bioinspired soft nanovesicles have been approved for clinical trials (ca. 28 globally) and many others (ca. 1705 active clinical trials) are under clinical investigation (L. L. W. Wang, Janes, et al., 2021). More importantly, in the clinical landscape, blood cells (RBCs, leukocytes, and platelets) and stem cells have demonstrated their better therapeutic performance globally as highlighted in Table 4. Further, T cells have a great portion of trials (ca. 45%) where T cells are capable enough to activate the immune cells and eradicate the cancer cells (L. L. W. Wang, Janes, et al., 2021).

In bioinspired soft nanovesicles based therapies, the patient themselves or other donors could be considered as the source of cells from which nanovesicles are obtained. On the other hand, platelets vesicles also play an important role in blood vessels by regulating hemostasis under normal conditions and thrombosis upon vascular damage. Further, allogeneic cells have been largely applied at clinical level. However, these allogeneic cells need (i) blood matching between donor and receiver and (ii) transfusion protocols to examine the cell durability (L. L. W. Wang, Janes, et al., 2021). It should be noted that bioinspired soft nanovesicles based therapeutic agents face the most common clinical translational challenges such as manufacturing challenges, biological challenges, and regulatory challenges

(L. L. W. Wang, Janes, et al., 2021). Moreover, biological activities, cell source, immunogenicity, safety, functional heterogeneity, and so forth are key features of these therapeutic agents. In addition, targeted delivery has been noticed as an another biological challenge for many bioinspired soft nanovesicles based therapeutic agents, particularly for solid tumor diagnosis and treatment. Next, developing cost effective, safe, and automated manufacturing processes are also challenging but these are necessary for the production of better quality therapeutic agents.

In terms of manufacturing challenges, first of all, cells are extracted/obtained from the patient and transported to the manufacturing site where these cell-derived nanovesicles are isolated, purified, activated, and genetically modified and then quality assurance and packing dose are taken care of before being dispatched to the site of preclinical and clinical trials. However, these therapeutic agents and their production face critical concerns of regulatory approval standards, and in 2020, US FDA has released a warning notice concerning the hazards of unapproved stem cell therapies (L. L. W. Wang, Janes, et al., 2021). Overall, several other parameters of cell-based products have major importance for translating the laboratory skilled cell-based therapeutics for further clinical trials/or studies.

5 | CONCLUSIONS AND OUR PERCEPTION

In current biomedical research, bioinspired therapeutic platforms have been recognized as potential systems for site-selective tumor treatment with low dose requirements. These systems have been documented in the literature with better biosafety, low side effects, and significant tumor growth inhibitions. Low product yield and poor reproducibility of these therapeutic agents are major challenges that need to be achieved with better procedures. So far, characteristics of surface biomarkers that identify the molecular contents of a particular type of cancer are poorly understood.

Here, in this review, we have introduced the functional design and an importance of bio-responsive soft vesicles for targeted imaging and therapeutic performances in preclinical models. In this review, we have discussed the major advantages of cell-derived vesicles over self-assembled soft vesicles like liposomal hybrids. Liposomal structures have been recognized as versatile and safe platforms for drug delivery, gene delivery, imaging, and cancer therapeutic applications, and even some of such formulations are in the clinical trials. These liposomal therapeutic systems suffer from sophisticated surface modification processes, poor targeting ability for a specific tumor or cell site, long-time retention in the liver and spleen, and low stability during blood circulation.

Next, various examples of cell-derived cellular therapeutic platforms for better-targeted imaging and therapies with their clinical relevance as compared to liposomal systems have been highlighted in this article. Naturally obtained cellular products such as exosomes have been discussed in detail with their therapeutic performance and targeted imaging applications. Fundamental understanding and biogenesis mechanism of exosomes have been addressed with different isolation/or collection and purification methodologies. Microscopic significance of exosomes has also been explained in brief. Understanding the importance of surface biomolecules available on the exosomal surface is an ongoing research area for early-stage diagnosis and therapeutics of cancer. Globally, many research groups have reported exosome-based systems for imaging and cancer therapeutic applications. Further, exosomes have also been reported for targeted nucleic acid delivery and biomarkers communication between two cells. It has been observed that the cell-derived exosomes are limited with low cargo capacity, poor reproducibility, and low scalability that hinder their preclinical or clinical translational applicability.

Herein, we have addressed a wide range of cell-based products with their therapeutic performances including their advantages and disadvantages. Recently, cell membrane-based nanosized ghost platforms has been applied for drug/gene delivery and oncomedicine applications. These bioinspired membrane nanovesicles named biological nanoparticles have major advantages over exosome-based systems in terms of stability, large cargo capacity, natural/inherent targeting ability, reproducibility, scalability, controlled particle size distribution, better uptake within tumor environment, and so forth. Due to these advantages of biological nanosystems, they demonstrate better diagnostic and therapeutic performances followed by easy penetration and long-time retention in solid tumor microenvironment without any side effect on surrounding healthy cells/tissues. Naturally available surface biomarkers improve the biocompatibility, blood circulation, specific bio-distribution, targeting ability, stability, and so forth of these bioinspired membrane nanovesicles "biological nanoparticles."

A comprehensive detail of biological hybrid materials has been covered with their physicochemical characterizations. Overall, these biological systems have shown better tumor-targeted imaging and significant tumor reduction with low dose administration. Apart from the foremost advantages and disadvantages of nanosized bio-responsive hybrid systems, precarious limitations of the traditional therapeutics process have also been highlighted. It has been realized

that the traditional therapeutic approaches need better replacement because of their nonspecific targeting, expensive and time taking procedures, and poor biocompatibility of used therapeutics drugs/or agents. Therefore, bioinspired nanosized platforms discussed in this review demonstrate their better diagnostic and therapeutic outcomes which have gained huge consideration for significant elimination of cancer cells. It has been noticed that type of cell source and the genetic engineering of cellular therapeutic probes play an important role in targeted anti-tumor activity. However, these therapeutics approaches are still facing major challenges such as (1) expensive methodologies for diagnosis and treatment, (2) low yield and purification of therapeutic agents, (3) long term toxicity, (4) poor understanding of natural targeting, (5) insignificant reduction of solid tumors, and (6) nonspecific bio-degradation and uptake of injected therapeutic platforms. Overall, addressing the above-mentioned critical limitations may gain attention for FDA approval of these treatment strategies.

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CONFLICT OF INTEREST

The authors declare no competing financial interest and no conflicts of interest for this work.

AUTHOR CONTRIBUTIONS

Rajendra Prasad: Conceptualization (equal); writing – original draft (equal); writing – review and editing (equal). **João Conde:** Conceptualization (lead); funding acquisition (lead); supervision (lead); validation (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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