Biomimetic Nanoparticles for Cancer Targeting and Drug Delivery

Sahil Malhotra, PhD
University College Dublin, Ireland; malhotrasahil8491@gmail.com

https://doi.org/10.57098/SciRevs.Biology.2.1.1
Received January 23, 2023. Accepted February 16, 2023

Abstract: Cellular membrane engineered nanoparticles (NPs) have shown immense potential for anti-cancer drug delivery applications. In principle, cell membrane of any type of cells can be processed to obtain purified cellular membrane which can self-assemble to form stable and highly robust nanovesicles. These nanovesicles retain lipid-bilayer architecture of host's cells and much of the surface biomarkers and proteins are conserved during top-down approach. Interestingly, nanovesicles have exhibited long plasma circulation and appreciable tumour specific binding, which is largely suggestive of their biomimetic properties. Many pioneer studies have demonstrated their ability to encapsulate different chemotherapeutic agents and photosensitizers of varied chemical complexities, and releasing them in a triggered fashion. Additionally, the novel NPs system has been developed for cancer immunotherapy. The review discusses some of the important research and applications of cellular membrane derived nanovesicles for different forms of cancer therapy and their potential to be developed as personalized nanomedicine.

Keywords: Cell membrane derived nanovesicles, chemotherapy, photothermal therapy, targeted delivery, cancer immunotherapy

Abbreviations: Nanoparticles- NPs, Polylactic-co-glycolic acid- PLGA, Polyethylene glycol- PEG, Doxorubicin- DOX, Paclitaxel- PTX, doxorubicin loaded pegylated liposomes- DOXIL

Introduction

Nanoparticles represents an important class of drug delivery systems due to their ability to increase the therapeutic efficiency of free drug formulations and to reduce their side effects (Tennyson 2012). It can significantly alter the pharmacokinetics of chemotherapeutic drugs and release them in a sustained or triggered fashion (Jinjun et al., 2017). Consequently, many different types of nanoparticles are clinically approved to treat different types of cancers (Daniel et al., 2016). In a quest to develop biocompatible and more effective drug delivery system than synthetic NPs, scientists have recently tried to engineer the hosts' own cells to derive nanoparticles for personalized nanomedicine (Ronnie Fang et al., 2017). The concept involves the sequential lysis of cells to obtain the purified cellular membrane after removal of their intercellular contents. It is further reduced in size during which process, it self-assembles into nanovesicles and can encapsulate drugs with varied chemical structures. Using this biomimetic approach, the resultant nanovesicles would be relatively less immunogenic and more biocompatible than the synthetic analogues since these NPs shared structural similarities with cells from which these were derived. (Brian et al., 2015). Because of their remarkable "stealth", these nanovesicles can evade immune recognition and hence show improved pharmacokinetics, which can dramatically increase accumulation of the encapsulated drugs at the tumour site due to enhanced permeability and retention (EPR) effects. Therefore, cell membrane derived NPs can be used to develop next generation and advanced drug delivery platforms for personalized drug delivery.

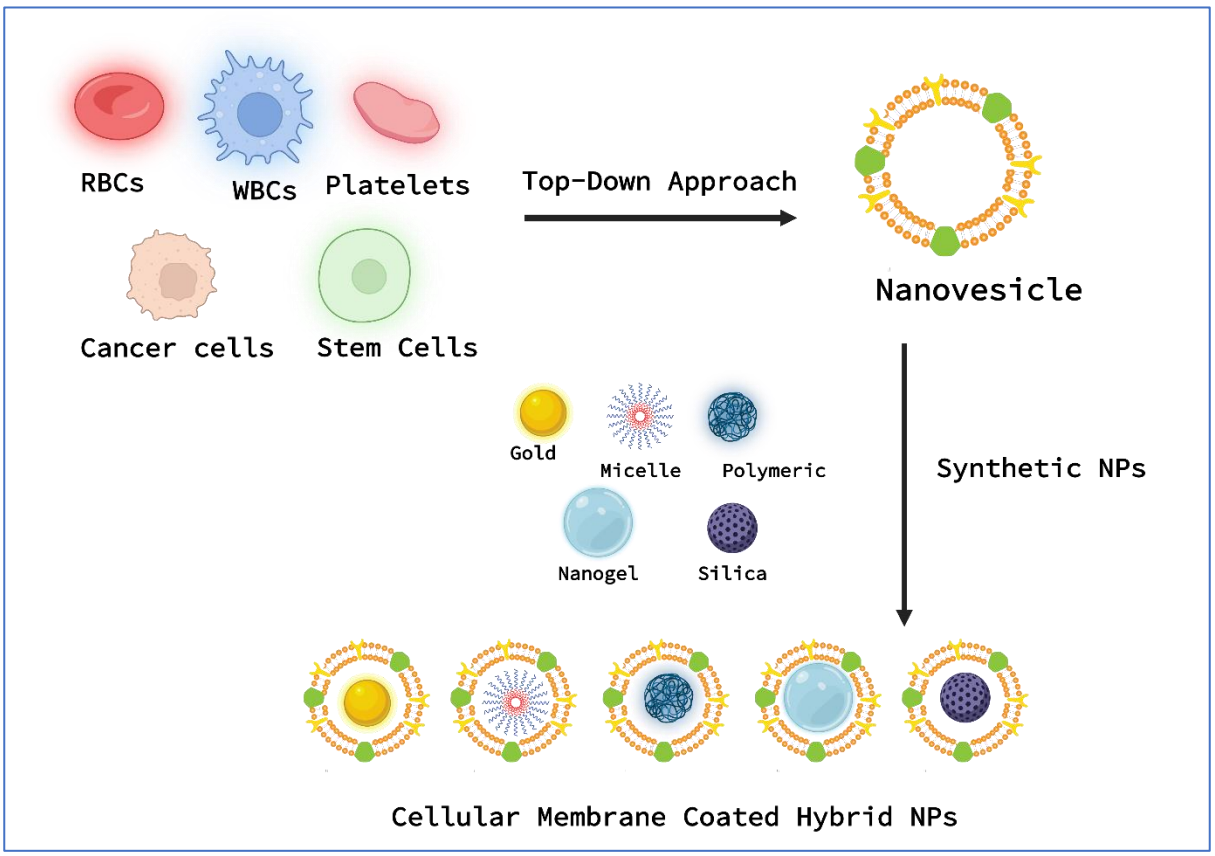

Figure 1: Schematic illustration of cellular membrane derived nanovesicles

Nanovesicles have been obtained from many different types of cells such as, RBCs, WBC, platelets, and even from cancer cells and stem cells (Pratigyan et al., 2020). Either these NPs can directly encapsulate the drugs, or the purified cellular membrane can be coated over synthetic NPs to form a hybrid drug delivery system (Pratigyan et al., 2020). In either way, it is possible to conserve the plethora of host specific biomarkers and proteins over the nanovesicle's surface which are normally present on the source cells (Figure 1). Importantly, Che-Ming et al. had shown that RBCs membrane can act as stealth coating over PLGA NPs, and can significantly enhance plasma circulation in comparison to PEG, which has been used as a gold standard to coat synthetic NPs in order to evade their immune recognition (Brian et al., 2015). Nanovesicles are obtained from purified membrane via top-down approaches. The easiest way to reduce size of cell membrane is through sonication, that uses ultrasonic waves to fragment the lipid bi layer, which can spontaneously reassemble to smaller sized nanovesicles. However, it is not a reproducible approach to derive nanovesicles and it generated more membrane fragments (Yuan et al., 2015). In order to derive reproducible nano formulations with low polydispersity and precise size range, cell membrane is extruded through polycarbonate membranes of fixed pores size (Yuan et al., 2015). Another lesser reported process involves microfluidic electroporation which involves membrane fragmentation of cells with electric current while flowing through microfluidic channels(Lang et al. 2017). Cellular membrane derived nanovesicles, irrespective of their cell source and the physico-chemical methods used for their formulation, mimic to larger extent to liposomes in morphology. These possess core-shell morphology, with proteins embedded in lipid bilayer surrounding an aqueous core, thus highly suitable to encapsulate both lipophilic and hydrophilic drugs simultaneously (Zehui et al., 2020). In this review, we highlight some of the recent developments in this field and describe the potential application of cell membrane derived nanoparticles for cancer therapy (Figure 2). Broadly, the NPs have been explored to deliver the chemotherapeutic drugs, photothermal/photodynamic agents and their combinations for dual therapy. Further their use for cancer immunotherapy has also been discussed in some detail.

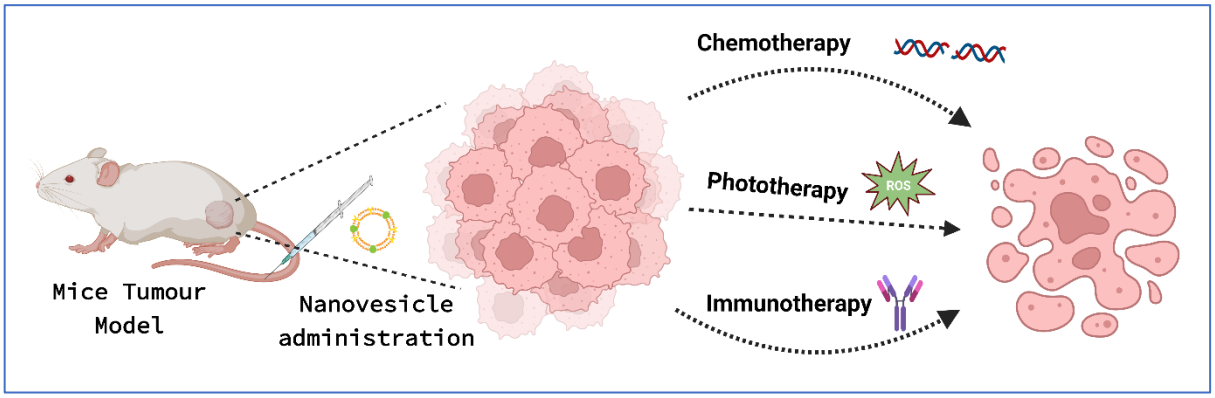

Figure 2: Applications of cellular membrane derived nanovesicles for cancer therapy

RBCs Derived Nanovesicles

The literature about the use of RBCs derived nanovesicles, hereby termed as Nanoerythrosomes (NER), for anti-cancer drug delivery dates back to the experiments conducted by Lejeune et al., who extruded erythrocytes and thereafter covalently linked daunorubicin with surface proteins. It showed significantly lesser clearance of drug through liver in comparison to similar sized liposomes, and thus a superior efficacy in animal studies. The field remained unnoticed for a longer time and it was until 2011, when Che-Ming et al. exploited RBCs membrane as alternative to PEG to coat poly lactic-co-glycolic acid (PLGA) NPs, which showed dramatic increase in plasma residence time of RBCs membrane coated NPs, which was later attributed to the preservation of CD-47, a "marker of self" on its surface. It inhibits phagocytosis by interacting with SIRPα complex on macrophage surface (Che-Ming., 2011). Since then, it has been extensively explored for cancer nanomedicine to encapsulate and deliver different combinations of drugs (Table 1). For instance, Nanoerythrosomes based formulations of many different chemotherapeutic drugs such as doxorubicin (DOX), paclitaxel (PTX), camptothecin (CPT), Fluorouracil, and their combinations with photothermal/photodynamic agents like indocyanine green (ICG), carbocyanine derivative (DiR), chlorin e6 (Ce6), perfluorocarbons (PFTBA), gold NPs have shown significant anti-tumour response in animal models(Qouc-Viet et al., 2018). In one study, it was shown that, RBCs derived nanovesicles can load DOX chloride via ammonium sulphate gradient, much similar to clinically approved liposomal nano formulation DOXIL (Xinxin et al., 2017). Their application is not just limited to smaller sized chemotherapeutic drugs, rather Nanoerythrosomes can also be used for gene therapy wherein, RBCs membrane-liposomal lipid bilayer fused hybrid NPs targeted human epidermal growth factor receptor 2 (HER2) positive cancers and selectively delivered DNA-aptamer-modified DNA tetrahedron (Wenjuan et al., 2022). Additionally it can also be used to prevent premature degradation of drug (Sahil et al.). Interestingly, much recently RBCs derived NPs have been shown to enhance therapeutic response of cancer immunotherapy. It works by harnessing hosts' immune capabilities to destroy cancer cells. Specifically, RBCs membrane was fused with tumour cell membrane and further processed to form tumour associated antigen (TAA) presenting NPs. The inherent properties of Nanoerythrosomes to be captured by macrophages and dendritic cells were leveraged and thus in this way, antigen presenting cells (APCs) were targeted effectively. It resulted in stronger T-cell mediated immune response in mice tumour model probably due to higher CD8-T cell infiltration (Xiao et al., 2019). Another interesting experiments were conducted by Guo et al., who utilized Nanoerythrosomes to deliver tumour specific antigen to target dendritic cells (DCs) and induce cytotoxic T lymphocyte (CTL) mediated response (Yuanyuan et al., 2015). The group encapsulated melanoma associated antigenic peptides in PLGA NP and subsequently coated it with RBCs membrane to enable prolonged circulation and present antigens directly to T-cells after processing by APCs. This nano vaccine produced much stronger and specific immune response against melanoma cells which resulted in higher tumour growth retardation and reduced metastasis in comparison to control sets of animals. In all these reports, Nanoerythrosomes have been shown to enhance

the therapeutic response of conventional anti-cancer therapy, supposedly because of their prolonged plasma circulation time and effective tumour accumulation. Unlike synthetic NPs, these nanovesicles can evade RES uptake by liver Kupfer cells for longer time, which is indicative of their "stealth" nature. It offers strong pharmacokinetics and thus more bioavailability of the drug molecules. Additionally, their unique physico-chemical characteristics enable encapsulation and protection of the sensitive chemotherapeutic drugs, which otherwise would undergo premature degradation at physiological conditions.

Table 1: List of applications of cell membrane derived nanovesicles for cancer therapy

Cell Source and Application	Therapeutic Agents	Methodology	Core Material	Outcomes	Ref
Red Blood Cells	DOX	Extrusion	PLGA NPs	Tumour growth retardation and increased overall survival of animals	Brian et al.
Chemotherapy	5-Fluorouracil	Extrusion	Chitosan/PLGA NP	Improved Pharmacokinetics and Biodistribution	Al Qahtani et al.
	Camptothecin	Extrusion	PEG-PCL Micelle	Increased therapeutic efficacy and reduced side effects	Sahil et al
Phototherapy	ICG	Extrusion		Decreased tumour growth rate due to thermal ablation of tissue	J.M. et al.
	Iron-Oxide	Microfluidic Electroporation	Iron-oxide NPs	Enhanced Phototherapy	Rao et al.
Chemo-Photothermal/Photodynamic Therapy	PTX/DiR	Extrusion	PCL	Suppression of the lung metastasis	Su et al.
Gene Therapy	DNA-aptamer	Extrusion	Self -assembled DNA aptamers	Increased tumour regression and reduced side effects	Wenjuan et al.
Immunotherapy	Tumour associate antigen (TAA)	Sonication		Stronger anti-cancer immune response	Han et al.
	Melanoma associated antigen	Extrusion	PLGA NPs	Stronger immune response	

Cancer Cells					
Chemotherapy	DOX	Extrusion	Mesoporous Silica NPs	Stronger anti-tumour response than DOXIL	Di Nie et al.
	DOX	Extrusion	Iron Oxide NPs	Homotypic binding and self-recognition to same cancer cell lines	Jing-Yi et al.
	Cisplatin	Extrusion	Gelatin NPs	Significant tumour targeting along with effective anti-tumour response and virtually no recurrence	Lang et al.
Photothermal Therapy	ICG	Extrusion	PLGA	Efficient accumulation at tumour site and effective photothermal effects	Ze Chen et al.
Chemo + Gene therapy	PTX-siRNA	Extrusion	PLGA	Excellent synergistic effects in mice models	Cong et al.
Immunotherapy	B16-F10 Melanoma derived antigens and CpG adjuvant	Extrusion	PLGA	Enhanced antigen presentation and activation of tumour specific immune response	Ashley et al.
	LuC-4T1 cells antigens and adjuvant	Sonication	PLGA	Nano vaccine elicited a stronger and personalized immune response	Xiang et al.
	Breast Cancer Cells Antigens	Extrusion	Dextran Coated Silicon	Promising adjuvant Properties	Flavia et al.
Platelets					
Chemotherapy	Bufalin	Sonication	PLGA	Active targeting	Haijun et al.
Chemo-phototherapy	DOX-polypyrrole	Extrusion		Active targeting and synergistic effects	Long et al.
Leukocytes					
Dual Chemo-Gene Therapy	DOX-siRNA	Extrusion	Lipid Nano vector	Improved tumour targeting and synergistic effects	Yali et al.
Neutrophils Control Metastasis	Carfilzomib	Extrusion	PLGA	Binding to CTCs and their apoptosis	Ting et al.
NK cells Immuno-Phototherapy	Porphine Derivative	Extrusion	mPEG-PLGA	Produced Macrophage polarization to induce anti-tumour immunity	Guanjun et al.
T-cells Photothermal Therapy	ICG	Extrusion	PLGA	Higher tumour affinity and therapeutic efficiency	Yutong et al.

Macrophages Chemotherapy Photothermal	DOX	Extrusion Extrusion	PLGA Au Nano shells	Camouflaging properties and efficient therapeutic efficiency Biocompatibility and efficient PTT	Minjun et al. Mingjun at al.
Stem Cells Bone Marrow derived mesenchymal stem cells	DOX	Extrusion	Gelatin	Improved therapeutic efficiency	Changyong et al.

Platelets Derived Nanovesicles

Platelets have remarkable ability to evade phagocytosis similar to that of RBCs probably due the presence of CD-47 on their surface (Quoc-Viet. 2018). It was used to coat PLGA NPs containing bufalin, an anti-neoplastic agent that can reverse multi-drug resistance and inhibit angiogenesis (Haijun et al., 2019). The NPs showed targeted binding to hepatoma cells due to interaction between p-selectin on platelets membrane and CD-44 overexpressed on cancer cells. In another report, platelet membrane derived NPs loaded DOX and photosensitiser polypyrrole NPs simultaneously for dual chemo-photothermal therapy (Long et al., 2020). It caused synergistic effect and tumour growth retardation in orthotopic hepatocellular carcinoma model. The NPs were biocompatible and ensured safety and efficacy for chemo-photothermal therapy. An interesting application of platelet membrane cloaking was for ferroptosis enhanced cancer immunotherapy (Qin et al., 2020). Ferroptosis is a cell death mechanism, quite different than apoptosis and necrosis, which is due to inactivation of glutathione peroxidase. It results in accumulation of oxidative species leading to lipid peroxidation and cell death. Some iron based NPs have shown potential to induce ferroptosis, but their application is limited due to their ready immune clearance and poor tumour targeting. Therefore in order to improve tumour targeting and localization, iron oxide NPs were coated with platelet membrane. These NPs were co-loaded with a potent ferroptosis inducing agent sulfasalazine. Iron oxide worked synergistically with the drug to induce ferroptosis. The NPs system showed effective tumour growth retardation and significantly reduced metastasis. Thus, platelets derived NPs are useful for tumour targeting and immune evasion essential for appreciable accumulation in tumour tissue.

Immune Cells Derived Nanovesicles for Cancer Therapy

Immune cells, called as leukocytes, comprise of different types of cells with unique functionalities. Similar to other cells membrane, synthetic NPs can also be coated with immune cells that enable them to acquire several functionalities (Zehui et al., 2020). Leukocytes derived NPs, termed as, leukosomes, are well equipped with surface functionalities that can specifically recognize tumour cells in addition to providing long plasma circulation. Thus, it can be a promising delivery vehicle to ensure tumour specific delivery of different drugs. For instance, Minjuan et al. demonstrated camouflaging properties of macrophage membrane coated silica NPs containing DOX as chemotherapeutic agent, which produced higher therapeutic response in mice 4T1 tumour model. In another study, macrophage membrane coated gold (Au) NPs were used for selective tumour targeting in a mice 4T1 breast cancer model and further explore it for photothermal therapy. It showed prolonged circulation and tumour specific targeting due to the presence of surface proteins on macrophage membrane. Upon laser irradiation, there was a strong tumoricidal response observed due to localized heating effects caused by gold NPs (Mingjun et al., 2016). Similarly, Yali et al. developed a gene delivery vector carrying LPCAT1 siRNA along with DOX and functionalize it with leukocytes membrane for targeted delivery to squamous oesophagus carcinoma (Yali et al., 2020). Leukocytes membrane functionalization enhanced the transmigration and chemotaxis of these nano vectors. The hybrid system produced synergistic anti-tumour effects in a mice xenograft tumour model.

Another interesting example includes the Natural Killer (NK) cells which are well-equipped with highly potent cytolytic tools that can precisely sense and eradicate tumour cells. Stimulated NK cells lyse

the tumour cells via multitude of mechanisms, mainly through their activating receptors (NKG2D, NKp30, NKp44, NKp80), or expression of apoptosis inducing ligands, such as against FAS/TRAIL receptors, and can also recognize monoclonal antibodies against tumour markers (Hans-Gustaf et al., 2007). Alternatively, NK cell mimetics, hereby termed "Nano bullets", are projected to outperform in terms of functional apoptosis efficiency since these cells free, nanometre sized, NKsomes, no longer require directional chemotaxis for tumour infiltration and migration (Chan-Hua et al., 2020). These cell free nano constructs have been derived from NK cell membrane, which retain much of the surface markers and hence, cytolytic properties of NK cells. NKsomes, unlike their precursors, can extravasate through leaky vasculature of solid tumours and can show relatively stronger retention and migration characteristics. For instance, NK cells membrane was coated over PLGA NPs encapsulating a photosensitizer for combined photo-immunotherapy (Guanjun et al., 2018). Some of the important activating receptors of NK cells were conserved onto NPs surface which could induce M1 macrophage polarization and dendritic cells maturation. Combined with the selective uptake by tumour tissue, upon laser irradiation, it produced pronounced cytotoxic response. In another interesting study, scientists utilized Neutrophils membrane derived NPs to neutralize circulating tumour cells (CTCs) and prevent metastasis (Ting et al., 2017). Neutrophils membrane functionalized PLGA NPS loaded with proteosome inhibitor carfilzomib, were able to bind with CTCs and induced apoptosis in these cells and could prevent metastasis. Conclusively, different types of immune cells can be engineered to derive stable nanovesicles that preserve surface functionalities of parent cells and enable tumour specific recognition and targeting.

Cancer Cell Membrane Derived Nanoparticles

Cancer cells are known to exhibit strong homotypic cell-cell adhesion which is mainly mediated by N-cadherin, carcinoembryonic antigen, etc (Ziling et al., 2020). Significant number of studies have demonstrated that much similar to RBCs membrane, cancer membrane can also be utilized to derive kinetically stable NPs and can also be coated over synthetic NPs to form a hybrid nanoparticle system (Zehui et al., 2020). Their application for drug delivery is based on the stronger homotypic cell binding exhibited by the cancer cells and thus the resultant cell membrane coated NPs could also show stronger and targeted tumour delivery. Ronnie et al. functionalized PLGA NPs surface with cancer cell membrane and studied their potential for cancer vaccine and for drug delivery. For proof of concept studies, the group selected the mouse melanoma cell lines as a model to obtain purified cellular membrane and showed that the resulting NPs retained much of the surface biomarkers specific to their source cells. These NPs delivered tumour associated antigens to dendritic cells, which subsequently stimulated T-cells to produce tumour specific immune response. In another interesting study, Jing-Yi et al. coated DOX loaded iron oxide NPs with different cell membranes and studied their self-recognition tendency *in-vivo* mice tumour models. Two different types of tumour models, namely murine hepatocellular carcinoma (H22) and human squamous epithelia (UM-SCC-7), were simultaneously developed in the left and right limbs of the mouse respectively. These tumour bearing mice were injected with NPs prepared by coating DOX/iron oxide NPs with hepatocellular membrane. After *in-vivo* administration, higher DOX accumulation was observed in the hepatocellular carcinoma, suggesting self-recognition and tumour-selective targeting of these nanoparticles (Jing-Yi et al., 2016). It further resulted in reduced tumour growth rate in animals injected with homotypic NPs prepared from the same source of cells. Similarly, cancer cells derived NPs can also be used to co-deliver a chemotherapeutic drug and gene editing tools simultaneously, which was demonstrated by the highly specific and targeted delivery of PTX and siRNA to homotypic cancer in mice (Cong et al., 2020). Extending the application of cancer cell membrane derived nanoparticles, MCF-7 cell membrane was coated over PLGA NPs encapsulating indocyanine green for photo diagnostics and phototherapy (Ze et al., 2016). Some of the important cell adhesion markers like EpCAM, N-cadherin, galectin, were shown to be descended from the source cells onto NPs surface during the top-down approach. The hybrid NPs system had shown reduced clearance through liver and kidneys, and prolonged tumour accumulation in comparison to uncoated NPs suggesting strong homologous binding.

Cancer cell membrane has immense potential to be used for cancer immunotherapy due to the presence of myriad of tumour associated antigens (TAAs) which can induce much stronger and specific immune response against cancer cells and thus can be utilized as cancer vaccines (Ziling et al., 2020). For this, cancer cells derived NPs can be the ideal

candidate due to the absence of nucleus and it retains most of the surface antigens. For instance, breast cancer cells derived membrane was coated over the silicon NPs functionalized with dextran for cancer immunotherapy (Flavia et al., 2017). The developed nano vaccine induced expression of immune stimulatory signals over the immune cells and secretion of inflammatory cytokines (Flavia et al., 2017). Thus, in addition to providing long circulation, cancer cells derived NPs can be utilized for active targeting due to their self-recognition tendency and the conservation of tumour associated antigens can make it suitable for cancer immunotherapy.

Stem-cells Derived Nanoparticles

Stem cells have been immensely utilized for regenerative medicine. In literature, there are fewer reports regarding utility of stem cells membrane for anti-cancer therapy. After being inspired by camouflaging properties of other cells types, scientists functionalized DOX loaded nanogels with bone marrow derived mesenchymal stem cells membrane (Chengyong et al., 2016). Compared to the uncoated nanogels, it demonstrated enhanced tumour targeting and accumulation, and thus significantly increased therapeutic efficiency and reduced side effects. In another study, umbilical cord derived MSCs were utilized to coat PLGA NPs encapsulating DOX and studied their therapeutic efficacy in a mice xenograft model (Yang et al., 2018). This system also showed enhanced tumour regression and fewer side effects attributed to low immunogenicity of MSCs membrane and efficient tumour accumulation of drug molecules.

Conclusion

It is clearly evident that nearly every type of mammalian cells can be harnessed to obtain purified cellular membrane which can then be engineered to load and deliver different therapeutic agents for targeted cancer therapy. Cell membrane can provide a stealth coating with low immunogenicity, thus can be superior to PEG and can be used as alternative to coat the synthetic NPs. The nanovesicles mimic to their parent cells in terms of structure and biochemical signatures. The choice of which cells to employ for cancer therapy largely depend upon the specific combination of therapeutic agents and type of tumour to be treated. It is worth exploring their scale up and clinical translation and it can emerge as a cutting edge and advanced carrier for drug delivery.

References

AlQahtani, S. A., Harisa, G. I., Alomrani, A. H., Alanazi, F. K., & Badran, M. M; Improved pharmacokinetic and biodistribution of 5-fluorouracil loaded biomimetic nanoerythrocytes decorated nanocarriers for liver cancer treatment. *Colloids and Surfaces B: Biointerfaces, 2021;* 197, 111380. https://doi.org/10.1016/j.colsurfb.2020.111380

Ashley V. Kroll, Ronnie H. Fang, Yao Jiang, Jiarong Zhou, Xiaoli Wei, Chun Lai Yu, Jie Gao, Brian T. Luk, Diana Dehaini, Weiwei Gao, and Liangfang Zhang; Nanoparticulate Delivery of Cancer Cell Membrane Elicits Multiantigenic Antitumor Immunity; *Adv. Mater. 2017,* 1703969. https://doi.org/10.1002/adma.201703969

Brian T. Luk, Liangfang Zhang; Cell membrane-camouflaged nanoparticles for drug delivery; *Journal of Controlled Release;* 220 (2015) 600–607. https://doi.org/10.1016/j.jconrel.2015.07.019

Burns, J. M., Vankayala, R., Mac, J. T., & Anvari, B; Erythrocyte-derived theranostic nanoplatforms for near infrared fluorescence imaging and photodestruction of tumors. *ACS Applied Materials & Interfaces, 2018,* 10, 27621–27630. https://doi.org/10.1021/acsami.8b08005

Che-Ming J. Hu, Li Zhang, Santosh Aryal, Connie Cheung, Ronnie H. Fang, and Liangfang Zhang; Erythrocyte membrane-camouflaged polymeric nanoparticles as a biomimetic delivery platform; *PNAS, 10980–10985, 2011, vol. 108*. https://doi.org/10.1073/pnas.1106634108

Chengyong Goa, Zhihua Lin, Beatriz Jurado-Sanchez, Xiankun Lin, Zhiguang Wu, Qiang He; Stem Cell Membrane-Coated Nanogels for Highly Efficient In Vivo Tumor Targeted Drug Delivery; *Small*, *2016*. https://doi.org/10.1002/smll.201600624

Chun-Hua Wu, Jingbo Li, Li Li, Jianping Sun, Muller Fabbri, Alan S. Wayne, Robert C. Seeger & Ambrose Y. Jong; Extracellular vesicles derived from natural killer cells use multiple cytotoxic proteins and killing mechanisms to target cancer cells; *Journal of Extracellular Vesicles 2019, Vol. 8*, 1588538. https://doi.org/10.1080/20013078.2019.1588538

Cong Xu, Wan Liu, Yuan Hu, Weiping Li, and Wen Di; Bioinspired tumor-homing nanoplatform for co-delivery of paclitaxel and siRNA-E7 to HPV-related cervical malignancies for synergistic therapy; *Theranostics 2020, Vol. 10, Issue 7*. https://doi.org/10.7150/thno.41228

Daniel Bobo, Kye J. Robinson, Jiaul Islam, & Kristofer J. Thurecht; Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date; *Pharm Res ,2016,* 33:2373–2387. https://doi.org/10.1007/s11095-016-1958-5

Di Nie, Zhuo Dai, Jialin Li, Yiwei Yang, Ziyue Xi, Jie Wang, Wei Zhang, Kun Qian, Shiyan Guo, Chunliu Zhu, Rui Wang, Yiming Li, Miaorong Yu, Xinxin Zhang,Xinghua Shi, and Yong Gan; Cancer-Cell-Membrane-Coated Nanoparticles with a Yolk−Shell Structure Augment Cancer Chemotherapy; *Nano Lett. 2020, 20,* 936−946. https://doi.org/10.1021/acs.nanolett.9b03817

Flavia Fontana, Mohammad-Ali Shahbazi, Dongfei Liu, Hongbo Zhang, Ermei Mäkilä, Jarno Salonen, Jouni T. Hirvonen, and Hélder A. Santos; Multistaged Nanovaccines Based on Porous Silicon@Acetalated Dextran@Cancer Cell Membrane for Cancer Immunotherapy; *Adv. Mater. 2017*, 1603239. https://doi.org/10.1002/adma.201603239

Guanjun Deng, Zhihong Sun, Sanpeng Li, Xinghua Peng, Wenjun Li, Lihua Zhou, Yifan Ma, Ping Gong, and Lintao Cai; Cell-Membrane Immunotherapy Based on Natural Killer Cell Membrane Coated Nanoparticles for the Effective Inhibition of Primary and Abscopal Tumor Growth; *ACS Nano 2018, 12,* 12096−12108. https://doi.org/10.1021/acsnano.8b05292

Haijun Wang, Junzi Wu, Gareth R. Williams, Qing Fan, Shiwei Niu, Jianrong Wu, Xiaotian Xie and Li-Min Zhu; Platelet-membrane-biomimetic nanoparticles for targeted antitumor drug delivery; *J Nanobiotechnol (2019) 17,* 60. https://doi.org/10.1186/s12951-019-0494-y

Hans-Gustaf Ljunggren and Karl-Johan Malmberg; Prospects for the use of NK cells in immunotherapy of human cancer; *Nature Reviews Immunology, Volume 7, May 2007.* https://doi.org/10.1038/nri2073

Jing-Yi Zhu, Di-Wei Zheng, Ming-Kang Zhang, Wu-Yang Yu, Wen-Xiu Qiu, Jing-Jing Hu, Jun Feng, and Xian-Zheng Zhang; Preferential Cancer Cell Self-Recognition and Tumor Self-Targeting by Coating Nanoparticles with Homotypic Cancer Cell Membranes; *Nano Lett. 2016, 16,* 5895−5901. https://doi.org/10.1021/acs.nanolett.6b02786

Jinjun Shi, Philip W. Kantoff, Richard Wooster and Omid C. Farokhzad; Cancer nanomedicine: progress, challenges and opportunities; *Nature Reviews, 2017, Volume17*. https://doi.org/10.1038/nrc.2016.108

Lang Rao, Bo Cai, Lin-Lin Bu, Qing-Quan Liao, Shi-Shang Guo, Xing-Zhong Zhao, Wen-Fei Dong, and Wei Liu; Microfluidic Electroporation-Facilitated Synthesis of Erythrocyte Membrane-Coated Magnetic Nanoparticles for Enhanced Imaging-Guided Cancer Therapy; *ACS Nano 2017, 11,* 3496−3505. https://doi.org/10.1021/acsnano.7b00133

Lang Rao, Guang-Tao Yu, Qian-Fang Meng, Lin-Lin Bu, Rui Tian, Li-Sen Lin, Hongzhang Deng, Weijing Yang, Minghui Zan, Jianxun Ding, Andrew Li, Haihua Xiao, Zhi-Jun Sun, Wei Liu, and Xiaoyuan Chen; Cancer Cell Membrane-Coated Nanoparticles for Personalized Therapy in Patient-Derived Xenograft Models; *Adv. Funct. Mater. 2019, 29,* 1905671 . https://doi.org/10.1002/adfm.201905671

Lejeune, A., Moorjani, M., Gicquaud, C., & Lacroix, J. (1994). Nanoerythrosome, a new derivative of erythrocyte ghost: Preparation and antineoplastic potential as drug carrier for. *Anticancer Research, 14,* 915–920

Long Wu, Wei Xie, Hui-Ming Zan, Zhongzhong Liu, Ganggang Wang, Yanfeng Wang, Wei Liu and Wenfei Dong; Platelet Membrane-Coated Nanoparticles for Targeting Drug Delivery and Local Chemo-Photothermal Therapy of Orthotopic Hepatocellular Carcinoma; *Journal of Materials Chemistry B; 2020*. https://doi.org/10.1039/d0tb00735h

Malhotra, S., Dumoga, S., Joshi, A., Mohanty, S., & Singh, N.; Polymeric micelles coated with hybrid nanovesicles enhance the therapeutic potential of the reversible topoisomerase inhibitor camptothecin in a mouse model. *Acta Biomaterialia, 2021,* 121, 579–591

Mingjun Xuan, Jingxin Shao, Luru Dai, Junbai Li, and Qiang He; Macrophage Cell Membrane Camouflaged Au Nanoshells for in Vivo Prolonged Circulation Life and Enhanced Cancer Photothermal Therapy; *ACS Appl. Mater. Interfaces 2016, 8,* 9610−9618. https://doi.org/10.1016/j.actbio.2020.11.049

Minjun Xuan, Jingxin Shao , Luru Dai , Qiang He , and Junbai Li; Macrophage Cell Membrane Camoufl aged Mesoporous Silica Nanocapsules for In Vivo Cancer Therapy; *Adv. Healthcare Mater. 2015*. https://doi.org/10.1002/adhm.201500129

Na Yang, Yanping Ding, Yinlong Zhang, Bin Wang, Xiao Zhao, Keman Cheng, Yixin Huang, Mohammad Taleb, Jing Zhao, Wen-Fei Dong, Lirong Zhang, and Guangjun Nie; Surface Functionalization of Polymeric Nanoparticles with Umbilical Cord-Derived Mesenchymal Stem Cell Membrane for Tumor-Targeted Therapy; *ACS Appl. Mater. Interfaces 2018, 10,* 22963−22973. https://doi.org/10.1021/acsami.8b05363

Pratigyan Dasha, Anna Maria Pirasb, Mamoni Dash; Cell membrane coated nanocarriers - an efficient biomimetic platform for targeted therapy; *Journal of Controlled Release 327 (2020)* 546–570. https://doi.org/10.1016/j.jconrel.2020.09.012

Qin Jiang, Kuang Wang, Xingyu Zhang, Boshu Ouyang, Haixia Liu, Zhiqing Pang, and Wuli Yang; Platelet Membrane-Camouflaged Magnetic Nanoparticles for Ferroptosis-Enhanced Cancer Immunotherapy; *Small 2020,* 2001704. https://doi.org/10.1002/smll.202001704

Quoc-Viet Lea, Jaiwoo Leea, Hobin Leea, Gayong Shimb,Yu-Kyoung Oh; Cell membrane-derived vesicles for delivery of therapeutic agents; *Acta Pharmaceutica Sinica B 2021;11(8)*. https://doi.org/10.1016/j.apsb.2021.01.020

Rao, L., Cai, B., Bu, L.-L., Liao, Q.-Q., Guo, S.-S., Zhao, X.-Z., Dong, W.-F., & Liu, W; Microfluidic electroporation-facilitated synthesis of erythrocyte membrane-coated magnetic nanoparticles for enhanced imaging-guided cancer therapy. *ACS Nano, 2017, 11,* 3496–3505. https://doi.org/10.1021/acsnano.7b00133

Ronnie H. Fang, Che-Ming J. Hu, Brian T. Luk, Weiwei Gao, Jonathan A. Copp, Yiyin Tai, Derek E. O'Connor, and Liangfang Zhang; Cancer Cell Membrane-Coated Nanoparticles for Anticancer Vaccination and Drug Delivery; *Nano Lett. 2014, 14,* 2181−2188. https://doi.org/10.1021/nl500618u

Ronnie H. Fang, Yao Jiang, Jean C. Fang, Liangfang Zhang; Cell membrane-derived nanomaterials for biomedical applications; *Biomaterials 128 (2017)* 69e83. https://doi.org/10.1016/j.biomaterials.2017.02.041

Su, J., Sun, H., Meng, Q., Yin, Q., Zhang, P., Zhang, Z., Yu, H., & Li, Y; Bioinspired nanoparticles with NIR-controlled drug release for synergetic chemophotothermal therapy of metastatic breast cancer. *Advanced Functional Materials, 2016,* 26, 7495–7506. https://doi.org/10.1002/adfm.201603381

Tennyson L. Doane and Clemens Burda; The unique role of nanoparticles in nanomedicine: imaging, drug delivery and therapy; *Chem. Soc. Rev., 2012, 41,* 2885–2911. https://doi.org/10.1039/c2cs15260f

Ting Kang, Qianqian Zhu, Dan Wei, Jingxian Feng, Jianhui Yao, Tianze Jiang, Qingxiang Song, Xun bin Wei, Hongzhuan Chen, Xiaoling Gao, and Jun Chen; Nanoparticles Coated with Neutrophil Membranes Can Effec tively Treat Cancer Metastasis; *ACS Nano 2017, 11,* 1397−1411. https://doi.org/10.1021/acsnano.6b06477

Wenjuan Ma, Yuting Yang, Jianwei Zhu, Weiqiang Jia, Tao Zhang, Zhiqiang Liu, Xingyu Chen, and Yunfeng Lin; Biomimetic Nanoerythrosome-Coated Aptamer–DNA Tetrahedron/Maytansine Conjugates: pH-Responsive and Targeted Cytotoxicity for HER2-Positive Breast Cancer; *Adv. Mater. 2022, 34,* 2109609. https://doi.org/10.1002/adma.202109609

Xiang Xiong, Jingya Zhao, Jingmei Pan, Chunping Liu, Xing Guo,* and Shaobing Zhou; Personal ized Nanovaccine Coated with Calcinetin-Expressed Cancer Cell Membrane Antigen for Cancer Immunotherapy; *Nano Lett. 2021, 21,* 8418−8425. https://doi.org/10.1021/acs.nanolett.1c03004

Xiao Han, Shufang Shen, Qin Fan, Guojun Chen, Edikan Archibong, Gianpietro Dotti, Zhuang Liu, Zhen Gu, Chao Wang; Red blood cell–derived nanoerythrosome for antigen delivery with enhanced cancer immunotherapy; *Sci. Adv. 2019.* https://doi.org/10.1126/sciadv.aaw6870

Xinxin Zhang, Pavimol Angsantikul, Man Ying, Jia Zhuang, Qiangzhe Zhang, Xiaoli Wei, Yao Jiang, Yue Zhang, Diana Dehaini, Mengchun Chen, Yijie Chen, Weiwei Gao, Ronnie H. Fang, and Liang fang Zhang; Remote Loading of Small Molecule Therapeutics into Cholesterol-Enriched Cell Membrane-Derived Vesicles; *Angewandte Chemie, 2017.* https://doi.org/10.1002/anie.201707598

Yali Jun, Zhuang Tang, Chao Luo, Baofei Jiang, Xiang Li, Mingyue Tao, Hao Gu, Lu Liu, Zhengwei Zhang, Su'An Sun, Kairong Han, Xiaojuan Yu, Xudong Song, Guoquan Tao, Xiaofei Chen, Li Zhang, Yong Gao, and Qi-long Wang; Leukocyte-Mediated Combined Targeted Chemo and Gene Therapy for Esophageal Can cer; *ACS Appl. Mater. Interfaces 2020, 12,* 47330−47341. https://doi.org/10.1021/acsami.0c15419

Yuan-Chia Kuo, Hsuan-Chen Wu, Dao Hoang, William E. Bentley, Warren D. D'Souza, and Srini vasa R. Raghavan; Colloidal Properties of Nanoerythrosomes Derived from Bovine Red Blood Cells; *Langmuir 2016, 32,* 171−179. https://doi.org/10.1021/acs.langmuir.5b03014

Yuanyuan Guo, DongWang, Qingle Song, Tingting Wu, Xiangting Zhuang, Yuling Bao, Miao Kong, Yan Qi, Songwei Tan, and Zhiping Zhang; Erythrocyte Membrane-Enveloped Polymeric Nanoparticles as Nanovac cine for Induction of Antitumor Immunity against Melanoma; *ACS Nano; VOL. 9,* NO. 7 , 6918–6933, 2015. https://doi.org/10.1021/acsnano.5b01042

Yutong Han, Hong Pan, Wenjun Li, Ze Chen, Aiqing Ma, Ting Yin, Ruijing Liang, Fuming Chen, Yifan Ma, Yan Jin, Mingbin Zheng,* Baohong Li,* and Lintao Cai; T Cell Membrane Mimicking Nanoparticles with Bioorthogonal Targeting and Immune Recognition for Enhanced Photothermal Therapy; *Adv. Sci. 2019, 6,* 1900251. https://doi.org/10.1002/advs.201900251

Ze Chen, Pengfei Zhao,⊥ Zhenyu Luo, Mingbin Zheng, Hao Tian, Ping Gong, Guanhui Gao, Hong Pan, Lan lan Liu, Aiqing Ma, Haodong Cui, Yifan Ma, and Lintao Cai; Cancer Cell Membrane−Biomimetic Nanoparti cles for Homologous-Targeting Dual-Modal Imaging and Photothermal Therapy; *ACS Nano 2016, 10,* 10049−10057. https://doi.org/10.1021/acsnano.6b04695

Zehui He, Yongtai Zhang, Nianping Feng; Cell membrane-coated nanosized active targeted drug delivery systems homing to tumor cells: A review; *Materials Science & Engineering C 106 (2020)* 110298. https://doi.org/10.1016/j.msec.2019.110298

Ziling Zeng and Kanyi Pu; Improving Cancer Immunotherapy by Cell Membrane-Camouflaged Nanoparticles; *Adv. Funct. Mater. 2020,* 2004397. https://doi.org/10.1002/adfm.202004397

Conflicts of Interest

The authors state no conflict of interest.