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CELL MEMBRANE COATED NANOCARRIERS - AN EFFICIENT BIOMIMETIC PLATFORM FOR TARGETED THERAPY

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Abstract:	Targeted therapy approaches have become the core of modern translational science and as an intriguing field, it is the solution of the conventional drug delivery problems that were once unanswered. Traditional methods of delivering drugs and therapeutics-faced issues of solubility, sustained release and not enough amount getting through the diseased site, for e.g a tumor. Various formulations of liposomes, polymers, dendrimers, etc have succeeded and made their way for clinical trials trying to enhance the pharamacokinetic and biodistribution of the drug. Many stealth coatings that includes hydrophilic polymers (PEG, chitosan, polyacrylamides, etc) can act as a covering around the nanoparticle that can shield the surface from aggregation, opsonization and evade immune system, thus considered in Generally Recognized as Safe (GRAS) category. Several other polymers such as poly-2-oxazoline, polyethylene oxide, PEG based surfactant (polysorbate-80), and zwitterionic phospholipids have also been tested for their antifouling properties. However, the polymer coating approach requires labour-intensive procedures and conjugation chemistries that often fail in mice model. Besides, due to immunogenicity and allergic reactions evoked by the PEG coated nanoparticles there was an urge to find biomimicking materials that can prove better as shielding agents which paved the way for cell membrane coated nanoparticles (CMCNPs) to come into the limelight. CMCNPs consists of a nanoparticle inner core covered by cell membrane that can be implicated in targeted drug delivery approaches, photothermal therapy and diagnosis or imaging making it a powerful theranostic tool. In this review, mode of preparation of CMCNPs, different sources of cell membranes (RBCs, WBCs, platelets, cancer cells, stem cells with some other unconventional sources) and nanoparticle cores that are employed have been thoroughly emphasized. In addition to this, advancements and limitations pertaining to this newly emerging field have been focused.
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Cover Letter

Dr. Mamoni Dash
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02/07/2020

Dear Editor,

Biotechnology Advances

We are honored to submit our review manuscript entitled "CELL MEMBRANE COATED NANOCARRIERS - AN EFFICIENT BIOMIMETIC PLATFORM FOR TARGETED THERAPY" for your consideration.

Targeted drug delivery approaches have open up new and exciting avenues for answering to the existing limitation of drug toxicity and compromised pharmacological behavior in the pursuit of nanomedicine. Various types of nanomaterials are being developed to target to the site of interest, amongst which cell membrane coated nanoparticle hold special promise for the field. In this review article, we have tried to summarize the various aspects of the engineered nanoparticles towards targeting by appropriate coating of the cell membrane. The article contains our opinion on conventional stealth properties of nanosystems and how the existing limitations can be countered by cell membrane coated nanoparticles. The various methods of preparing such particles and their apt characterization are also described along with the various types of cell membranes that have been used for coating. Finally the numerous studies that have employed these coated nanoparticles for targeted therapy with successful culmination into patents and possible products are summarized.

Biotechnology Advances is a great platform that offers its readers exciting literature reviews on various fronts of biotechnological developments. Hence, we are hopeful this manuscript with its contents will be interesting to a wide range of scientists especially, those working on nanosystems and nanomedicines for regenerative medicine application.

This article is not under consideration elsewhere and is not published on web as well.

We hope the article will meet the high standards of the journal of Biotechnology Advances.

With best regards,

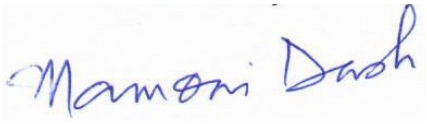
Mamoni Dash

Mamoni Dash

Conflict of Interest Form

It is hereby declared that there is no conflict of interest involved with the submission of this review manuscript.

Mamoni Dash



CELL MEMBRANE COATED NANOCARRIERS - AN EFFICIENT BIOMIMETIC PLATFORM FOR TARGETED THERAPY

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Abstract

Targeted therapy approaches have become the core of modern translational science and as an intriguing field, it is the solution of the conventional drug delivery problems that were once unanswered. Traditional methods of delivering drugs and therapeutics-faced issues of solubility, sustained release and not enough amount getting through the diseased site, for e.g a tumor. Various formulations of liposomes, polymers, dendrimers, etc have succeeded and made their way for clinical trials trying to enhance the pharamacokinetic and biodistribution of the drug. Many stealth coatings that includes hydrophilic polymers (PEG, chitosan, polyacrylamides, etc) can act as a covering around the nanoparticle that can shield the surface from aggregation, opsonization and evade immune system, thus considered in Generally Recognized as Safe (GRAS) category. Several other polymers such as poly-2-oxazoline, polyethylene oxide, PEG based surfactant (polysorbate-80), and zwitterionic phospholipids have also been tested for their antifouling properties. However, the polymer coating approach requires labour-intensive procedures and conjugation chemistries that often fail in mice model. Besides, due to immunogenicity and allergic reactions evoked by the PEG coated nanoparticles there was an urge to find biomimicking materials that can prove better as shielding agents which paved the way for cell membrane coated nanoparticles (CMCNPs) to come into the limelight. CMCNPs consists of a nanoparticle inner core covered by cell membrane that can be implicated in targeted drug delivery approaches, photothermal therapy and diagnosis or imaging making it a powerful theranostic tool. In this review, mode of preparation of CMCNPs, different

sources of cell membranes (RBCs, WBCs, platelets, cancer cells, stem cells with some other unconventional sources) and nanoparticle cores that are employed have been thoroughly emphasized. In addition to this, advancements and limitations pertaining to this newly emerging field have been focussed.

1. Introduction

Drug delivery approach is the process of delivering therapeutic molecules to a target tissue/cell type. The main area of drug delivery is concerned with route of administration, distribution, absorption and elimination of the drug by the body. Traditional drug delivery approaches relied on systemic circulation of the "naked drug" delivered by oral, intravascular, parenteral, inhalations and topical methods. These methods succumb to some limitations inside the body as the drug enters the systemic circulation with more than 90% of the drug is eliminated by renal clearance. Protein/peptide and gene based drugs are also prone to enzymatic and acid degradation. Therefore, carrier mediated or smart drug delivery approaches became popular that leads to maximum deposition of the drug in the diseased site leading to Targeted drug delivery systems (TDDS). Nanoparticle aided systems (nanotechnology) mainly aims on controlled (for prolonged period of time) and sustained release (steady release) of drugs leading to it's maximized plasma half life. Nanoparticles (NPs) are particles that fall in nanometer range (upto 1000 nm) which can serve as a single entity capable of coming in different sizes and morphology. Some of the most frequently used nanoparticles for research purposes are: biodegradable polymers, lipids, dendrimers, micelles,iron-oxide nanoparticles, silica nanoparticles, gold nanoparticles, carbon nanotubes and metallic nanoparticles. Liposomes are synthesized from lipids and cholesterol and resemble natural lipid bilayer membranes having the ability to encapsulate both water soluble and insoluble compounds. Polymeric nanoparticles are highly stable and biocompatible; the best example is poly (lactic-co-glycolic acid) being approved by U.S F.D.A. Carbon nanotubes and QDs are still in the infancy of the research and needs thorough study for any definitive conclusion. These aforementioned nanoparticles protect the drug from enzymatic degradation, increase the pharamacokinetic profile and prevent drug leakage to any other sites than the desired location without much affecting the normal cells per se. Encapsulation of small molecule inhibitors, chemotherapeutic drugs, siRNA, miRNA, inside nanoparticles can improve their biodistribution and can enhance the solubility issues. As a matter of fact, some of the drug- NP combinations like doxil (Dox-liposome), PEGasparginase, Ferumoxides, etc have emerged as a

paradigm for targeted drug delivery system by getting approved by U.S F.D.A (Narain et al., 2017). Targeted drug delivery systems (TDDS) mediated by nanoparticles can have a wide range of advantages that includes 1) sparing the healthy cells, 2) reducing the dosage thus combating the adverse effects of the drug molecule, 3) facile synthesis of surface conjugable moieties on nanomaterials due to nano size and high surface area per unit volume 4) transport of sparingly water soluble compounds to the diseased site. There are some key points for a successful targeted drug delivery system: retain, evade, target and release. First, there should be proper assurance of the amount of drug loaded onto the delivery vehicle, second it must bypass the immune cells leading to a long durability of circulation in blood and third reaching the site of interest and, should release the drug at the specific site without compromising the effective drug concentration of drug needed to bring an effect for proper drug functioning (Kumari et al., 2016).

Depending on the need, there are two strategies of TDDS: passive and active targeting. Passive targeting heavily implies on the EPR effect (Enhanced Permeation and Retention), coined by Matsumura and Maeda for the first time in the mid 1980s. Nanocarriers harness thier property of leaky microvasculature and extravasate into the neoplastic tissue that allows molecules of $\geq$ 600 nm inside the interstitial space due to the poorly aligned defective endothelial cells. This phenomenon is termed as the famous EPR effect. The most important lacuna of passive targeting is cell-specific interactions, a pre-requisite of nanoparticles internalization into targeted cells, thus decreasing the therapeutic efficacy needed to move for multiple dosage regimens and thus drug resistance (Gottesman et al., 2002) .For this purpose, eventually active targeting strategies were studied actively to deliver therapeutics to accurate sites that relies on tuning surface functionalities for delivering therapeutics (be it gene, drug or imaging agents) thus avoiding the healthy cells, increasing therapeutic index without any side effects. There are certain antigens that are very specific to tumor cells and are not present on normal cells. Interaction between the cancer specific receptors and ligand designed nanoparticles leads to controlled internalization of the nanoparticles inside the cells and thus deposition of drugs.

The targeted delivery of drugs via a drug carrier-based platforms has infact been proven fruitful when coated with various polymeric molecules that can be used as a protective covering more like a stealth mode to render it biocompatible. Stealth coatings of polymer around nanoparticles can reduce immunogenicity and make it less toxic to cells. By chemically decorating the nanoparticle surfaces

either by coating or conjugating polyethylene glycol (PEG) polymers, protein adsorption can be reduced to a large scale and therefore can be an effective tool as a therapeutic delivery vehicle. These PEG chains provide overall hydrophilicity and protein adsorbtion due to charge effect is drastically reduced (Shen et al., 2018). Proteins are basically sterically restricted from the solvents occupied by chemically non reactive polymers and are concentrated until further precipitation occurs (Atha and Ingham, 1981). However, development of nanocarriers to meet a specific need still remains a challenge. An emerging alternative to PEG can be Poly-2-oxazolines (POX) due to anti-PEG antibodies found as a common problem being reported by Garay *et al*., 2012 (Garay et al., 2012). POx (poly(2-methyl-2-oxazoline, PMeOx) has been used as popular option against conventional stealth coatings for a viral mediated nanoparticle system(Bludau et al., 2017) . However, these stealth coats, along with some other polymers (discussed in the succeeding section) eventually are being questioned for their utility as a good protective covering since it is being immunogenic and may raise the issue of allergic reactions. To combat this problem, many scientists have worked recently on cell membrane-based nanoparticles (CMBNPs). Following this study, many works related to biomimetic coatings have come to limelight employing various other cell membrane sources and diverse nanoparticles to avoid any kind of rejection from body (Li, R. et al., 2018). Nevertheless, biomimetic coatings on nanoparticles increases the chance of maximum release of payload to a destined target due to the inbuilt receptors that are present on the cell membrane itself that helps in proper targeting to desired cell, taking into account the homotypic (identical cell types) or heterotypic adhesions (different cell types) enabling cell-level targeting. The adhesive interactions however play a crucial role in cancer cells for tumor cells dissemination and metastasis to secondary sites with the help of certain cell adhesion molecules on the cancer cell membrane. The cell adhesion molecules appear to have role in adhering to similar cancer cells (homologous) or their extracellular matrix in secondary sites. This concept is basically taken when homologous targeting is thought of in TDDS. (Gao and Zhang, 2015)

2.Conventional stealth coatings

Nanoparticles are considered as foreign materials and due emphasis is always given by scientists to make it more amenable as “self” and consequently not cleared by the immune system. Previously and even currently, various strategies are being carried out to make nanoparticle a bio-friendly material. In context to this, trials have been made to coat nanoparticles with non reactive or inert polymeric

materials (natural and synthetic) that does not interact with the host's immune cells and thereby imparts a stealth or a cloak to the nanoparticles helping the foreign material (nanoparticles) to refrain evoking the host's (patient) immune system (Suk et al., 2016). The coatings used for cloaking nanomaterials can be either natural and semisynthetic. Among natural polymers, mostly polysaccharides originating from nature has been used, they are: dextran, polysialic acid, hyaluronic acid, chitosan (CS) and heparin while synthetic polymers are human made that include polyvinyl pyrrolidone (PVP), polyacrylamide (Pam), poly(ethylene glycol) (PEG), and PEG-based copolymers such as poloxamers, poloxamines, and polysorbates (Salmaso *et al*., 2013). Amongst natural sources, dextran is commonly applied over NPs. Nath *et al* in 2008 worked on dextran coated Au NPs for detecting antimicrobial susceptibility (Nath et al., 2008). In 2017, Kim *et al* worked on sialic acid modified AuNPs for evading immune system as sialic acid is considered as the marker of self.(Kim et al., 2017) According to Lu *et al*., 2019 chitosan coated PLGA nanoparticles resulted in controlled release of paclitaxel and high uptake efficiency in MDA-MB-231 cells.. The reason for using chitosan as a coating material is due to its positive charge at low pH because of protonating amino groups. This property leads to mucosal adhesion of chitosan coated nanoparticles and thus escape from reticuloendothelial system(Lu et al., 2019). In 2018, self assembled hyaluronic acid –chitosan NPs have been developed by Rho and team for treatment of insulin resistance in type 2 diabetes (Rho et al., 2018). PEG coated NPs rescued from the opsonization and macrophages uptake as compared to CS coated NPs as was evident by the study of Garcia *et al*., 2005 (Garcia-Fuentes et al., 2005) However, PEG coating did not do well in in vivo experiments and CS formulation escaped the immune system.

According to Nag *et al*., 2013, surface decoration of nanoparticles (here, for instance a liposome is shown in the figure below) with PEG moieties (PEGylated liposome) can be attained in two ways(Nag and Awasthi, 2013):

- by physically adsorbing PEG onto the surface of the vesicles (the process is physisorption): simply a coating procedure in which PEG solution is added to nanoparticle mixture.
- by introducing the PEG-lipid conjugate while the liposome is being prepared (includes pre-modification and co-incorporation method) or by covalently attaching reactive groups/ligands onto the surface of prefabricated liposomes (post modification method), as shown in the fig

below. (Fig.1) Conjugation chemistries include carbodiimide crosslinking chemistry, maleimide thiol conjugation, etc.

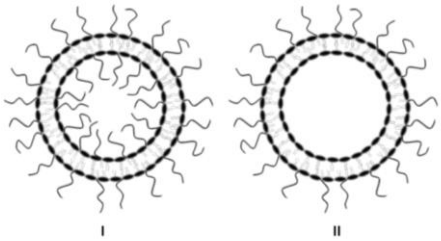


Fig.1. PEG moieties conjugated on liposomes either by pre modification method and post modification method to avoid internal space being hindered as in Pre insertion method and thus affecting drug loading efficiency (Nag and Awasthi, 2013). Adapted with permission from Nag et al.(2013).

Despite such advances of PEGylation, there has been a rising issue of immune response being directed against PEGylated proteins, drugs and nanomaterials. In 2018, Neun and coworkers published a work on anti PEG antibodies and complement activation against PEGylated liposomal doxorubicin (Neun et al., 2018). It has been found that repetitive administration of PEGylated therapeutics, including PEGylated asparaginase (Armstrong *et al*., 2007) elicit an immune response (anti-PEG antibodies has been detected by flow cytometry and sandwich ELISA) (Garay *et al*., 2012) (Armstrong et al., 2007; Garay et al., 2012) . The anti-PEG however detected can also be from previous exposure to PEGylated products (Hoang Thi et al., 2020). These coated NPs led to faster elimination by RES and eventually a poorer biodistribution profile. Also, in an effort to reduce the anti-PEG response, a more hydrophilic polymer and highly biocompatible material than PEG has been chosen i.e. poly-2-oxazoline. Experiments have been conducted on poly(2-methyl-2-oxazoline or PMeOx) to validate the hypothesis. One such study has been done by Bludau *et al* in 2017 to surface modify PMeOx on TMV(Bludau et al., 2017). They successfully proved that PMeOx is more water soluble than PEG. In this paper, POxylated nanoparticles showed lesser cellular uptake than the

PEGylated versions due to higher density of polyoxazolines on the TMV particles, however there was rapid clearance of naked TMV particles in comparison to surface modified TMV with POx5000 i.e. with longer chain. It was found that POxylated TMVs had a lesser antibody recognition than PEGylated and naked TMVs. Various efforts have also been made to use other polymers as alternative stealth coatings. For instance, PEO (Polyethylene oxide) modified polycaprolactone particles(Shenoy and Amiji, 2005), Poly(phosphazene) NPs modified with PEO copolymers (Vandorpe et al., 1996), Torchilin *et al* in 1994 studied on vinyl polymers that affected circulation time of liposomes in vivo(Torchilin et al., 1994) . In 2018, Chen and co workers worked on NMOFs (metal organic framework NPs) that were modified by nucleic acid aptamer sequence conjugated to polyacrylamide hydrogel for controlled release of the drug doxorubicin (Chen, W.-H. et al., 2018). Similarly, Moffat *et al* in 2003 made a novel polyacrylamide based magnetic nanoparticle for MRI imaging (Moffat et al., 2003). Polysorbate-80 modified CS NPs has been also evaluated for toxicity in in vivo model studied on brain localization, in the year 2015 by Yuan *et al*.(Yuan et al., 2015). PVP modified AuNPs showed enhanced retention time in blood confirmed by Mohamed and others in the year 2017 (Mohamed et al., 2017). According to Jiang *et al*., 2010, zwitter ionic phospholipids such as phosphobetaine, sulfobetaine or carboxybetaine moieties can prove as better antifouling agents since they can bind to proteins to a very lesser extent and thus avoid RES(Jiang and Cao, 2010).Vigorous trials have been put into efforts to improve the residual time of nanoparticles and it needs due consideration on the molecular weight and density of the polymeric coat. To overcome the tedious job of conjugating polymers on the surface of nanoparticles employing different strategies, cell- based nanoparticles are developed. This biomimetic method is becoming increasingly popular as a stealth material on NPs that contains a layer of innate proteins on the membrane making homing to a target cell easier and evading the immune system acquiring the property of "*disguised as self*". Cell membrane camouflaged NPs emerged in order to compensate for the traditional drug delivery strategies that included ligand modifications which were laborious, complex including many criteria and that too inefficient (Li, R. et al., 2018). Inspired by the nature, total cell membranes can be pulled out and can be ligated to design over the nanoparticle cores to endow them the intrinsic property to hide from the engulfing phagocytes and also membranes present over the surface of membrane coated NPs helps in homotypic mediated targeting, thus a bonus of both passive and active targeting. In fact, PEGylated nanoparticles can also be coated with cell membranes to increase the residual time of NPs in blood circulation. (Ochyl et al., 2018)

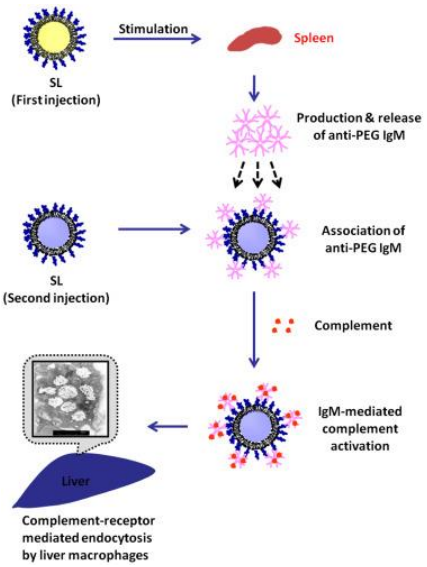


Fig.2. A schematic depicting the IgM production when a first dose of stealth PEGylated liposome is administered via a T-cell independent manner and then subsequently complement activation upon second injection.(Yang and Lai, 2015) Adapted with permission from Yang et al. (2015).

Basic concept of cell membrane coated nanoparticles (CMCNPs)

The story first began using RBC membrane as a coating onto nanoparticles by co extrusion method which was reported in the year 2011 Zhang and the team 2011(Hu et al., 2011) .The CMCNPs were made by fusing red blood cell (RBC) membrane that served as outer shell and a poly (lactic-*co*-glycolic acid) (PLGA) inner core, via a co-extrusion process, forming an intact core-shell structure .The basic structure of a cell membrane coated nanoparticle consists of a nanoparticle core (may be a liposome, polymer, inorganic particles) that are wrapped with membranes derived from cells to which they are basically targeted and then functionalize it with any other ligands, if necessary, shown in Fig.3.

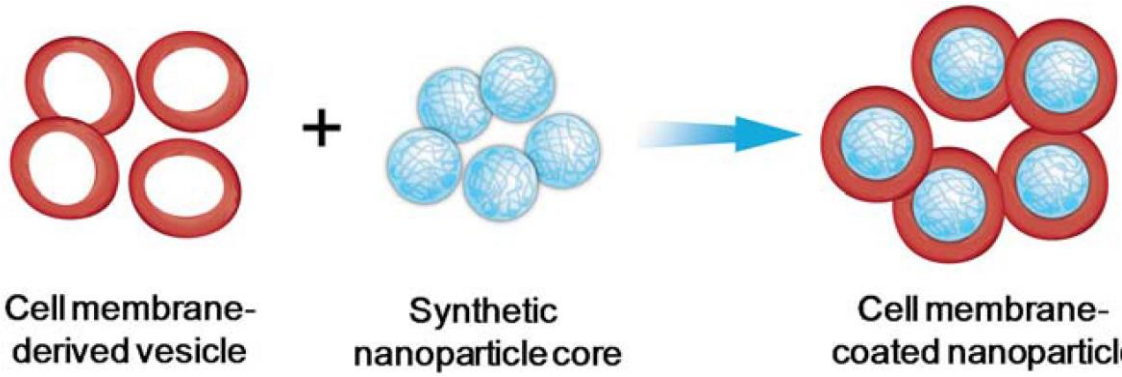


Fig.3. Representation of basic constituents of Cell membrane coated nanoparticles (CMCNPs) (Angsantikul et al., 2015) . Adapted with permission from Angsantikul et al.(2015). Copyright © 2015 by the authors; licensee MDPI, Basel, Switzerland.This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/). Articles from Vaccines are provided on the courtesy of Multidisciplinary Digital Publishing Institute (MDPI)".

Targeted delivery of drugs via core composed of different material and further coated with polymer or not often leads to severe immune responses. To compensate for this loss, a more autogenous option has been exploited. Cell membranes are used in the place of the synthetic polymers so as to avoid recognition by immune system as these are the self antigens that are present over the nanoparticle surface and nevertheless to achieve high targeting efficiency. The proteins present on the cell membranes bind to cells with the same membrane due to homotypic/heterotypic interaction (Li, R. et al., 2018). Hence, it can be better interpreted that CMCNPs can be both passive (avoiding RES and high retention time) and active targeted (due to the innate proteins that bind to the adhesion proteins on the desired cell of interest (Gao and Zhang, 2015). In addition, there is a whole lot option left to choose from a variety of material cores and cells whose membrane is to be chosen, according to the need: detection or targeting.

PEGylation or PEG coating onto nanoparticles is a bottom up approach that cannot meet the requirements of large batch production (Yao et al., 2019) whereas the cell membrane coating is a facile technique. Coating of cell membranes is a top down approach that mainly relies on the cell membrane to be used for coating without giving much attention to nanoparticle core, since the coating decides the nanoparticles to remain autogenous and protects from accelerated blood clearance (ABC) phenomenon (Fang et al., 2018). Till now, various cell membranes have been taken for coating such as: RBC, WBC, platelets, stem cells, bacteria, etc, all of which will be discussed vividly. Cell membrane coating can be beneficial for various other purposes besides drug delivery such as image guided photothermal therapy or simply Photodynamic therapy (PDT) , **immune modulation** or **detoxification** (Yao et al., 2019), (Ren et al., 2016), (Wei et al., 2018), (Li et al., 2014).

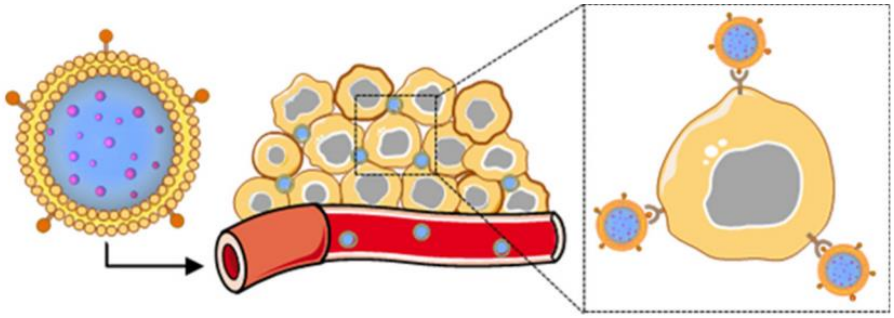


Fig.4. An illustration of cancer cell membrane coated nanoparticles binding to cancer cell more effectively due to homotypic binding and also escapes from blood vessels giving proof of stealth property(Harris et al., 2019). Adapted with permission from Harris et al.(2019).

Types of cell membranes for coating nanoparticles

Apart from RBCs, various other cells have been taken into account depending on the therapeutic functions needed that includes: RBCs, WBCs, platelets, stem cells, cancer cells and other unconventional sources. Material cores that are taken into account are biodegradable polyester NPs (PLA, PLGA, PCL), mesoporous silica NPs, magnetite NPs, gelatin and UCNPs. Cancer cells have been cloaked into PLGA nanoparticle core for cancer targeting (melanoma) (Fang, R. H. et al., 2014), stem cell coated PLGA NP for efficient targeting of orthotropic breast cancer(Tian et al., 2019a), macrophage coated mesoporous silica NPs as a biomimetic platform (Xuan et al., 2015). Neutrophil cloaked NP for delivery of chemotherapeutic agents has been developed to cure recurring glioblastoma and in some cases inhibiting synovial membrane inflammation and ease joint damage in inflammatory arthritis condition(Xue et al., 2017), (He, Y. et al., 2018b). RBC membrane coated NP absorbed toxins released from staphylococcus (alpha-hemolysin (Hu et al., 2013). Not only this, other NP cores can also be employed for vast therapeutic implications. Yang *et al* in 2019 made a cancer cell membrane shell and a core made up of silica nanoparticles encapsulating a photodynamic agent, Chlorin e6, for effective

photodynamic therapy(Yang et al., 2019). Lipid coated gold nanoparticles have been implemented in drug delivery, diagnostic and sensing (Hamilton et al., 2017). Understanding this, it is clear that various nanoparticle cores can be taken as vast as the cell membranes and can be extrapolated to innumerable possibilities in TDDS listed in Table 1 and picturized in Fig.5.

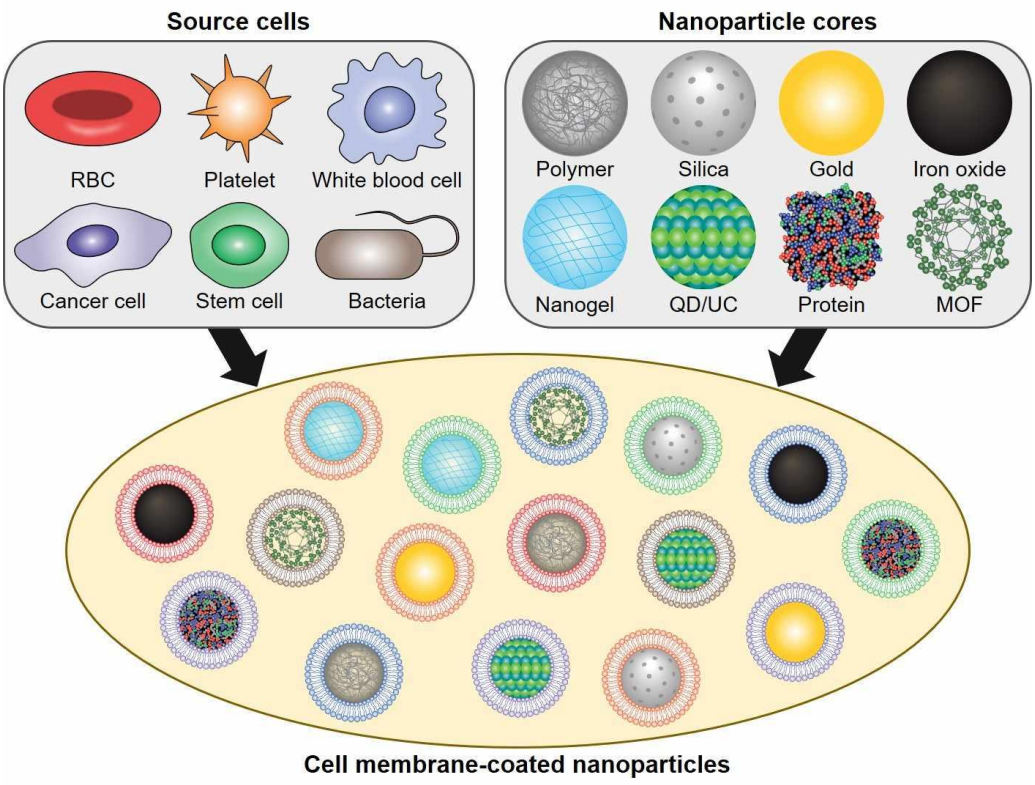


Fig.5. Source cells and nanoparticle cores can be merged and gives rise to CMCNPs for vast number of therapeutic applications(Fang et al., 2018). Adapted with permission from Fang et al. (2018).

Table. 1. Cell membrane type with typical characteristics and inner nanoparticles core employed for the delivery of therapeutics. *Lab tests=Both in vitro and in vivo work.

Cell membrane type	Uniqueness	Inner cores	Status
Red blood cell	Enhanced circulation	Liposomes	Lab test (Xie et al., 2019)
	Time (50 days in mice)	PLGA	FDA(Chen, Y. et al., 2018)
	Evading immune response	UCNs	Lab test (Li, M. et al., 2020)
		Gold NPs	Lab test (Zhu et al., 2018)
		MSN	Lab test (Xuan et al., 2018)
		PFCs	Lab test (Gao et al., 2017)
White blood cell	Homologous targeting	PLGA	Lab test (Kang et al., 2017)
	To leukocytes and	PLGA-lipid	Lab test (Han, Yutong et al., 2019)
	endothelium homing to inflamed zones	Liposome	Lab test (Pitchaimani et al., 2018)
	immune evasion		
Platelets	Homing to damaged prone	PLGA	Lab test (Song et al., 2019)
	Immune evasion	PLGA- CS	Lab test(Wang, Haijun et al., 2019)
	Long circulation time (10 days)	Polypyrrole	Lab test(Wu, Long et al., 2020)
		Au nanostars	in-vitro (Kim et al., 2020)
		PLGA	clinical (Hu et al., 2015)
Cancer cell	Cancer cell targeting and	PLGA	In vitro(Fang, Ronnie H. et al., 2014)
	Cancer antigen presentation	MSNs-PEG-lipid	Lab test (Nie, Di et al., 2020)
	Or cancer immunotherapy	PBAE NPs	Lab test (Zhang et al., 2020)
		Gelatin	Lab test (Rao et al., 2019a)
		Magnetic NPs	in-vitro(Bu et al., 2018)
		Silica	Lab test (Zhang, J. et al., 2019)
		Porphyrinic-MOFs	in-vitro (Zhang, D. et al., 2019)

Mesenchymal	Long circulation time Tumor targeting	Gelatin	Lab test (Gao, C. et al., 2016)
		PDA-Fe3O4	Lab test (Mu et al., 2018b)
		PLGA	Lab test (Bose et al., 2018)
		MSN-UCNPs	Lab test (Gao, Changyong et al., 2016)
Bacterial cell	Recognizes MAMPs and inhibition of pathogen adherence	AuNPs	Lab test(Gao et al., 2015)
		PLGA	Lab test(Zhang, Y. et al., 2019)
Fibroblasts	Homotypic targeting Immune evasion	Semiconducting polymeric NPs	Lab test (Li, J. et al., 2018)
Hybrid cells	Dual mode advantage	Polypyrrole	Lab test (Liu, Yao et al., 2018)
		Melanin	Lab test (Jiang et al., 2019)
		Liposomes	Lab test (He, Hongliang et al., 2018)

4. Preparation and techniques of characterization of CMCNPs

The preparation process of cell membrane coated NPs include two important protocols namely: Isolation of membrane fragments (or vesicles) and vesicle /membrane and nanoparticle fusion. Membrane vesicles are the most popular choice in comparison to membrane fragments as fusion of fragments to particles may not necessitate the presence of all the proteins required.

4.1. Isolation of cell membranes

In case of RBCs, which are devoid of nuclei, not much processing is required and the isolation procedure is straightforward. The isolated RBCs are cleared from buffy coat and serum and then repeatedly rinsed with PBS followed by centrifugation for getting rid from unwanted cells and plasma, if any. The RBC vesicles are then made to be free from hemoglobin by high speed centrifugation following sonication and passed through polycarbonous porous membranes (preferably 100 nm) to get definite size RBC vesicles. RBC vesicles can be stored at 4 °C for preservation (Su et al., 2017), (Hu et al., 2013). The second step is fusing membrane vesicles with nanoparticles.(Hu et al., 2011), (Fang, R. H. et al., 2014) The process of membrane isolation for platelets is similar to RBCs as platelets are also devoid of nucleus (Wang, H. et al., 2019), (Wu, L. et al., 2020). Complex eukaryotic cells like WBCs, cancer cells, stem cells, etc undergo thorough complex biochemical procedure that includes a combinational approach compiling ways such as hypotonic lysis, ultrasonication along with discontinuous sucrose density centrifugation to completely make the cell vesicle void of intracellular contents (Fang et al., 2018),(Cao et al., 2016),(Rao et al., 2017). Other ways of achieving membrane extraction other than hypotonic lysis includes: repeated freeze-thaw cycles, physical homogenization and electroporation technique). In freeze-thaw method, cells are placed in frozen state at -80°C followed by thawing at 37°C or in room temperature condition. The ice crystals formed as a consequence of repeated cooling leads to membrane disruption(Harris et al., 2019). Electroporation relies on the exposure of cells to electrical fields, as a result of which pores are created that causes membrane semi permeability(Rao et al., 2017), (Tsong, 1991). However, this method may also lead to changes or fluctuations in membrane potential. By far the most convenient method of cancer cell membrane extraction includes the hypotonic buffer treatment followed by mild sonication for membrane disintegration and sucrose density centrifugation to completely remove the nucleus and other intracellular components. Eventually, the membranes are passed through polycarbonate membranes in order to achieve a vesicle of desired size(Fang et al., 2018) . For cancer cells, mild lysis with greater speed via ultracentrifugation is needed as compared to RBCs, and these differences occur due to size, granularity and lipid bilayer of cells, which is unique for each cell type.

4.2. Fusion of membrane vesicles to the core NPs

The core nanoparticles synthesized can be fused to membrane vesicles by different methods, the major aim is to create the nanoparticles-membrane fusion with the membrane being oriented in the right side out position with all the receptor proteins exposed (Harris et al., 2019). Most of these methods rely on the net attraction between the oppositely charged molecules between the inner core particle and the membrane vesicle thus forming a core-shell structure with the proteins of the membrane facing towards right-side out conformation. (Zhai et al., 2017)

Co extrusion method in which the nanoparticle solution and the vesicle is co-extruded (passed through porous membranes) and sonicated for a couple of minutes to get CMCNPs of fixed cross sectional profile (Hu et al., 2015). Cancer cell membrane coated nanoparticles are produced by physical extrusion of both inner core material (PLGA) and cell membrane (MDA-MB-231cell line)(Chen et al., 2019). Extrusion generates a force strong enough to disrupt the structural integrity of membrane followed by reformation around the inner core nanoparticle (Zhai et al., 2017).

a. ***Sonication***: Sonication uses ultrasonication energy with specific frequencies to fuse membrane and nanovehicles.(Copp et al., 2014)

b. ***Microfluidic electroporation***: Fe3O4 NPs when mixed with RBC vesicles in a microfluidic chip where the electromagnetic energy creates pores in the cell membranes to the extent where the dielectric field on the cell membrane gets imbalanced. These pores help the Fe3O4 NPs to get the site of entry to be coated by vesicles. This method is becoming increasingly popular among scientists, as the stability of nanoparticles is not hindered preventing agglomeration. (Rao et al., 2017)

c. ***Cell membrane-templated polymerization:*** a relatively new technique and less explored which is dependent on interfacial interactions between the core and cell membrane. The polymeric core is grown *in situ* within the cores for efficient coating and easy manipulation of nanoparticle size where as in conventional method, preformed polymers are used and one cannot take control over already formed nanoparticles. Zhang and coworkers prepared acrylamide polymers within the vesicles and stopped the polymerization reaction outside the vesicle by using an inhibitor i.e. (2, 2, 6, 6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), a

popular membrane-impermeable free radical unstable molecule conjugated to PEG to inhibit passage of small molecules across the membrane. (Zhang et al., 2015)

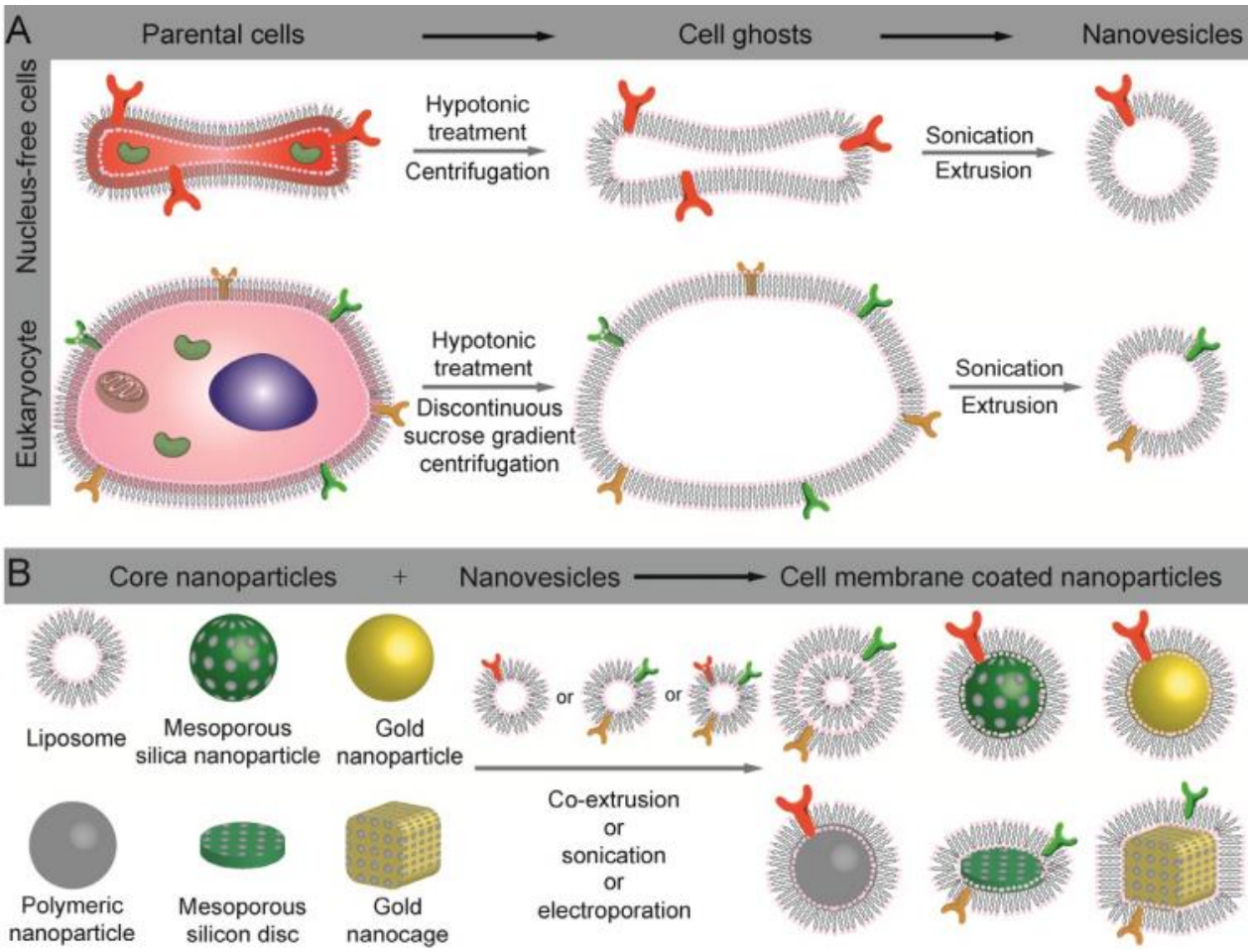
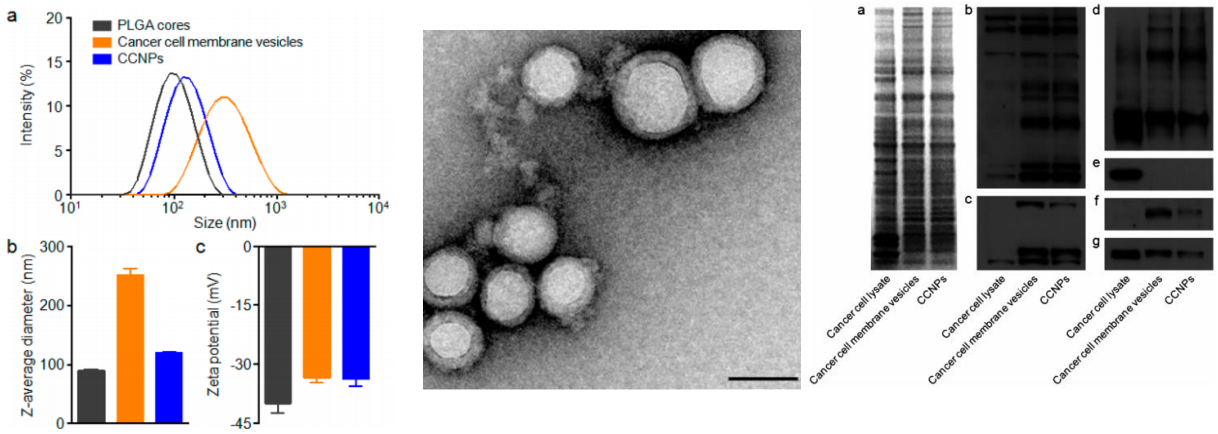


Fig 6. A) Summary of the methodologies adapted for preparation of CMCNPS. A)preparation of RBC coated NPs (Non-nucleated cell) while cancer cells and other nucleated cells undergo combinational approaches other than hypotonic lysis such as discontinuous sucrose density centrifugation B|) fusion of core NP with cell membrane which is similar for all cell types(Zhai et al., 2017). Adapted with permission from Zhai et al. (2018). This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY-NC) license (https://creativecommons.org/licenses/by-nc/4.0/).Copyright ©Ivyspring International Publisher".

4.3. Characterization of CMCNPs

The CMCNPs, thus produced needs characterization that includes some standard physicochemical procedures such as Transmission electron microscopy (TEM), Dynamic light scattering (DLS). Generally from TEM, the morphology of coated nanoparticles shows a halo around the bare NPs where as uncoated NP do not show such features. Also, RBCNPs shows an increase in size of 8 nm of what would be expected of thickness of RBC membrane. In addition, the surface charge is also an indicator to characterize CMCNPs. An uncoated PLGA nanoparticle with zeta potential of −35.9 mV, where as a RBC coated NPs shows zeta potential of around −28.3 mV, almost similar to the zeta value of RBC membrane vesicles(Ben-Akiva et al., 2020).This tells that the zeta potential of the final CMCNPs formed should be similar to membrane vesicles as the membrane vesicles are the one that are coated onto nanoparticle (Harris et al., 2019). Flow cytometric analysis can be helpful in tagging antibody (any antibody that is unique for each cell type) for example CD47 for RBCs and reading the signal fluorescence signal becomes relatively higher for CD47 when RBCNPs are stained with CD47 antibody(Ben-Akiva et al., 2020). Another confirmatory analysis can also be performed for validation i.e. western blotting that confirms the coated membrane. Samples are resolved by SDS-PAGE and then transferred to Nitrocellulose membrane followed by incubation with CD47 antibody, a marker specific for RBC membrane (CD47, CD41, p-selectin for Platelets)(Wang, H. et al., 2019).A band on these wells suggest positive for right side-out coating of membrane vesicles (Li, R. et al., 2018).Similarly, Cancer cells are also validated with western blotting looking for membrane-specific proteins (sodium-potassium pumps, pan cadherins) and taking some nuclear (histone) markers, intracellular markers to confirm that there is right side-out orientation of proteins in membrane coated nanoparticle formulation. (Fang, R. H. et al., 2014). All the above criteria for chacterization is also true for WBCs, stem cells and platelets –membrane coated nanoparticles. (Kang et al., 2017), (Gao, Changyong et al., 2016; Wang, H. et al., 2019) .

Preparation and characterization procedures are universal and well generalized protocols that can be used. Simple procedures can be adapted like electron microscopy (SEM, TEM), flow cytometry, Western blotting and Dynamic light scattering to confirm and characterize the CMCNPs.(Yao et al., 2019) .



i **ii** **iii**

Fig .7. Typical characterization of cancer cell membrane coated nanoparticles (CCMNP) i. Size comparison and zeta potential of PLGA core, vesicles and CCMNP, lesser size of coated formulation than vesicle itself shows the translocation of membrane onto NP, Zeta potential of coated NP is almost equivalent to vesicle. ii) Representative TEM image of multiple CCMNPs showing the halo around the nanoparticle. iii (a). Coomassie blue staining of cancer cell lysate, CCMNPs and vesicles showing protein bands. (b). Western blotting of Pan cadherin which is common in all the three wells, c. Sodium-potassium -ATPase pump marker(d) gp100 (transmembrane protein) (e) Histone H3 (a prominent nuclear marker), (f) cytochrome c oxidase (a mitochondrial marker) and (g) glyceraldehyde 3-phosphate dehydrogenase (a cytosolic marker), strong bands of membrane specific proteins on CCMNPs proves successful right side out fabrication.(Fang, R. H. et al., 2014)"Adapted with permission from Fang et al.(2014). https://doi.org/10.1021/nl500618u- Cancer Cell Membrane-Coated Nanoparticles for Anticancer Vaccination and Drug Delivery,Copyright © 2014 American Chemical Society.

5. Contribution of CMCNPs in Targeted therapy

Cell membrane coated NPs are well constructed for targeting to tumors and disease specific sites and that is an advantage when it comes to TDDS. Drug delivery platforms employ stealth nanosystems that can remain hidden in the body for a long duration without evoking the immune system delivering the drug to the target sites effectively. CMCNPs serve the purpose well, as they are innate and self to the system as well as home to the target sites efficiently because of the homotypic binding criteria (in cancer cells) and the self markers present on blood cells provide added benefit. Some of the model drugs that have been used in CMCNPs have shown wide benefits in disease targeting ability. The list

of some drugs used for treating certain disease models are shown in Table.2. To study the aspects of cell membrane coated NPs in details, we have to refer to the next section.

Table 2. List of some model drugs encapsulated in CMCNPs with the disease models

Model drugs	**Inner Core/Type of coating**	**Disease Model**
Doxorubicin	Iron oxide NPs/ cancer cell	Osteosarcoma(Huang et al., 2018)
Vincristine	SLNs/RBCs	Glioma (Fu et al., 2018)
Paclitaxel	PCL NPs and Pluronic F68/Cancer cell	Breast cancer(Sun et al., 2016)
Metmorfin	$W_{18}O_{49}$NPs/ Platelet	Burkitt's lymphoma(Zuo et al., 2018)
Paclitaxel	PLGA/stem cell	Orthotopic breast cancer(Tian et al., 2019b)
Doxorubicin	PLGA/Monocyte	Breast cancer(Krishnamurthy et al., 2016)
Doxorubicin	Copper sulphide/RBC and melanoma	Melanoma(Wang et al., 2018)
Cisplatin	Gelatin NPs/ HNSCC patient derived cell	HNSCC(Rao et al., 2019b)
Saikosaponin	PLGA/Macrophage membrane designed with T7 peptide	Breast cancer(Sun et al., 2020)

5.1. RBC membrane coated Nanoparticles (RBCNPs)

RBCs are the predominant blood cell in humans that function in transporting oxygen to all the body sites via hemoglobin. RBCs are easy to isolate being abundant in the blood and can circulate in the blood as evident in the *in vitro* systems (Chen, Y. et al., 2018; Han et al., 2018). RBC coated NPs are the first amongst all the CMCNPs, being chosen as a delivery vehicle due to the presence of self marker, CD47, CD59, complement factor 1, decay accelerating factor, C8 binding protein, etc. that evade the immune system (Hu et al., 2013; Hu et al., 2011; Narain et al., 2017). Barclay and co workers in 2014 made very clear that CD47 on the RBC membrane generates a "do not eat me" signal as the receptor interacts with **a**lpha (SIR Palpha) which is a signal regulating protein present on the macrophages (phagocytes) as a result of which the NPs escape the reticuloendothelial system (Xia et al., 2019). However, for effective internalization of RBCNPs into tumor cells, it requires certain ligands to be functionalized on it. Chemical methods may hamper the intact proteins on the membrane and can lead to unsatisfactory results. Fang *et al* suggested a lipid insertion approach that includes a lipid tethered ligand moieties that are functionalized onto RBC membranes, the ligands

being folate and a nucleolin-targeting aptamer, AS1411, that have variable molecular weights (Fang et al., 2013). Guo *et al* developed a mannose modified RBC coated PLGA NPs for targeting APCs in the lymph (Guo et al., 2015). In this way, ligands can also be functionalized on RBCNPs. Facile conjugation of various ligands can be done either with the help of chemical moieties or lipid tethering. These modified RBC membranes are then used for coating onto NPs with enhanced internalization capabilities PLGA NPs have been coated with RBC membrane vesicle for prolonging residence time in blood by Hu *et al* in 2011(Hu et al., 2011). Bidkar *et al* developed PLGA NP coated with RBC membrane carrying anticancer agent, doxorubicin and a photodynamic agent, methylene blue and further conjugated with Tf ligand for maximum internalization to MCF-7 and Hela cells. Chemotherapy coupled to photodynamic therapy (apoptosis of cells due to chemotherapy and ROS production by laser irradiation) caused enhanced anti proliferative effect. There was no much significant reduction of IC50 in case of Tf conjugated RBCNPs and RBCNPs but in flow cytometric data, it was made clear that Tf conjugated RBCNPs carrying drug and MB exhibited apoptosis to a higher extent. The experiments were also conducted in 3D spheroids after successful attempts in 2D monolayer cells. In 3D spheroid model also, Tf conjugated RBC coated NPs exhibited higher penetration ability as evidenced in CLSM and fluorescence intensity. In addition, when 3D spheroids were treated with, marked declining of IC50 was noticed that showed the synergistic effect of the two components encapsulated inside the RBC-Tf coated PLGA NPs, proving success in chemotherapy coupled photodynamic therapy (Bidkar et al., 2020).

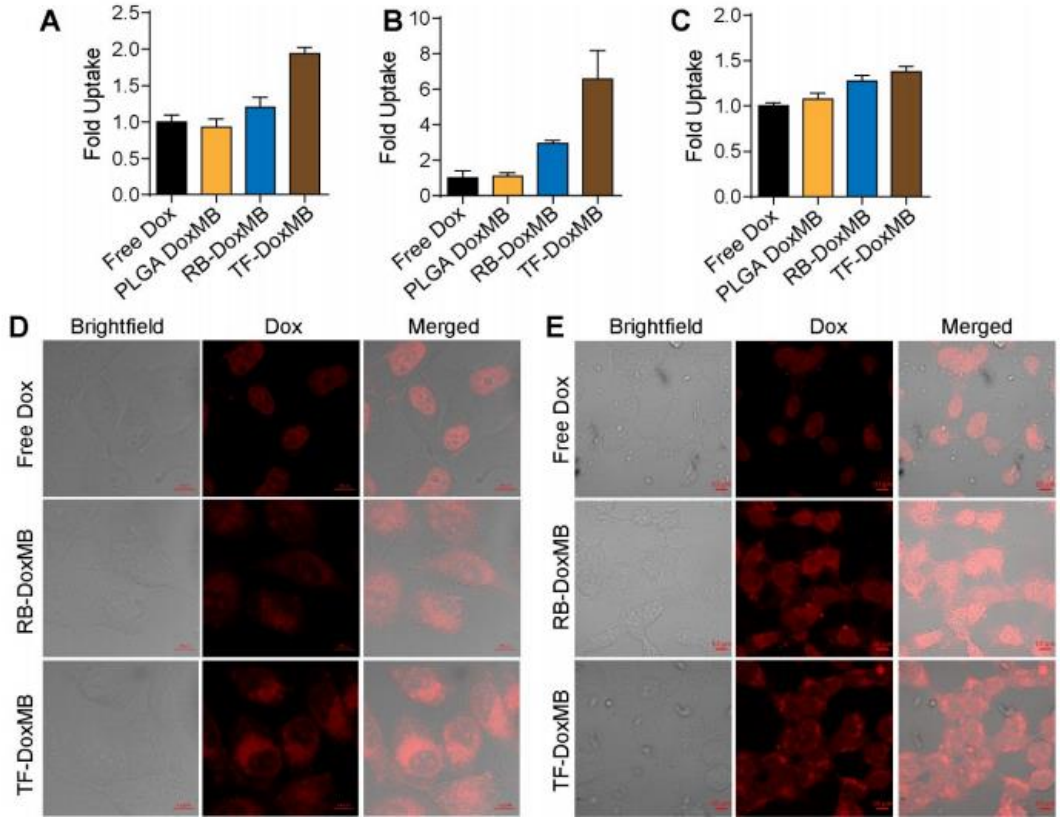


Fig.8. Flow cytometric data revealed that Hela cells (A) and MCF-7 (B) cell showed a 2 and 6 fold higher uptake capacity than non cancer cell line (1,3 fold for HEK293 cell) (C). D and E represents fluorescence microscopy images of Free dox that shows most accumulation in nucleus, however Tf conjugated RBC@Dox-MB showed enhanced accumulation in cytoplasm , as seen in merged images(Bidkar et al., 2020) . Adapted with permission from Bidkar et al. (2020).

Zhu *et al*., designed RBC coated gold nanocages modified with Epcam antibodies loaded with paclitaxel for targeted chemo and photothermal therapy (exposing to NIR radation) against 4T1 cancer cells with cell viability reduced to a larger extent (survival % being 25 %), thus RBC-Epcam antibody targeted Au nanoparticles could effectively target to tumors (high expression of Epcam antigen) delivering the drug, NIR laser being at 2.5 W/cm2(Zhu et al., 2018). Li et al worked on DSPE-PEG-FA-conjugated RBC coated up-conversion (UC NPs) by hypotonic treatment and extrusion method for multimodal imaging of Triple negative Breast Cancer using 4T1 as the model breast cancer cell line .The RBC@FA conjugated UC NPs helped in MRI, PET imaging in vivo

model. (Li, M. et al., 2020) Recently, Li and co-workers, developed a RBC coated Pluronic-F127 encapsulating Ag2S quantum dots also carrying the anticancer drug PEITC (phenethyl isothiocyanate) could effectively reduce the tumor in *in vivo* model and Ag2S QDs by generating oxygen in tumor region for sonodynamic therapy. H202 production was monitored and it intensified to 1.15±0.17 mmol/g and GSH was decreased to 1.33 ±0.26 μmol/g, thus alleviating colon cancer by generating ROS inside tumor cells. (Li, C. et al., 2020)

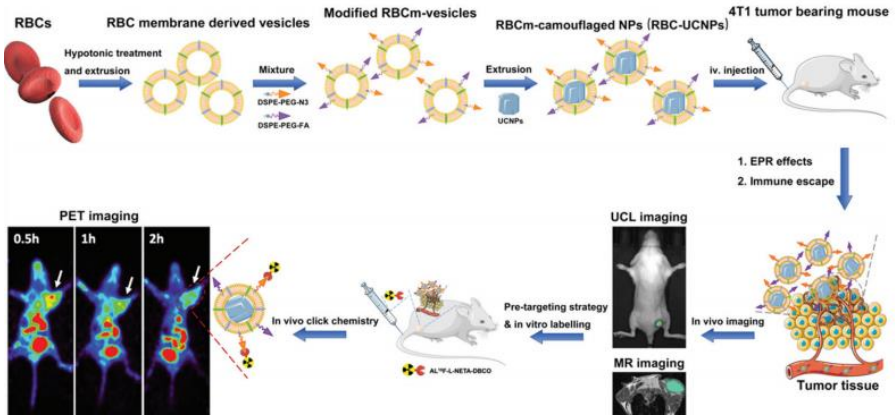


Fig.9. Diagrammatic illustration showing the RBC@FA conjugated UC NPs with optical properties helped in MRI and UCL imaging in *in vivo* tumor model(Li, M. et al., 2020). Reproduced from Ref. 48 with permission from the Royal Society of Chemistry.

It is now clearly understood that RBC has a long life span and an innate mechanism of evading the RES of body, which can be well implicated in targeting, imaging and various forms of photodynamic therapy apart from only conventional drug delivery purposes.

5.2. White blood cell membrane coated Nanoparticles (WBCNPs)

Along with RBC, WBCs or leukocytes are also potential cells that can be harnessed for camouflaging NPs. Since RBCs have a long life span of 4 months (around 120 days), the inherent stealth property has been a boon to translational biology, however RBCs lack a targeting property and often needs conjugating chemical groups or ligands to make it more precise or penetrable into desired cells. Therefore, WBCs having inherent homing (circulating in the blood stream) property to tumor and inflammation sites, they are also more recently employed for coating into nanoparticles(Huang et al., 2018). White blood cells have five major types according to granularity and morphology that includes: monocytes/ macrophages, neutrophils, eosinophils, basophils and lymphocytes, but few of

them can actually be translated as drug delivery platforms that is described in this section. Macrophages can home to inflammation and tumor sites, hypoxic areas following chemo-attractants such as CSF-1 (colony-stimulating factor) and chemokine-ligand-2 (CLCL-2) (Dong et al., 2017) . Sun *et al* developed a macrophage coated PLGA NP which carries the intrinsic macrophage membrane proteins (transmembrane and peripheral proteins) conjugated to T7 peptide that has the ability to bind to Transferrin receptors that are restricted to tumor cells. Macrophages (RAW 264.7) were selected due to the tumor/ inflammation homing ability. The macrophage coated NP encapsulated Saikosaponin D (SsD) which is a triterpene saponin abundant in *Bupleurum falcatum* with steroid like properties and acts as antitumor agent by apoptosis (Sun et al., 2020),(Chen, M.F. et al., 2016). *In vitro* cytotoxicity and cell uptake profile of the three cell lines, LO-2 (normal human liver cell line), RAW-267, 4-T1 and MCF-7, suggested the drug (SsD) loaded macrophage membrane coated nanoparticle (SMNPs) exhibited higher uptake in tumor cells (MCF-7 and 4-T1) and weaker fluorescence observed for RAW-267 and LO-2. Similarly, the SMNPs had higher cytotoxic effect to cancer cells and no much toxicity to normal cells than bare PLGA NP and only SsD. From *in vivo* experiments, it was found that there were less pulomonary metastatic nodules in SMNPs treated group. *In vitro* toxicity was also monitored with PBS and SMNPs. Heart, liver, spleen, lung and kidney showed no differences in pathology after 1 month. The SMNPs treated mice had diminished levels of phosphorylated versions of Akt and Erk protein, clearly depicting that the Akt signalling pathway was the plausible target of the SMNPs.

Neutrophils are the first WBC that are recruited or polarized to the site of injury/inflammation or tumor through transmigration process due to the presence of various adhesion molecules like LFA-1 and Beta-1 integrin serving the purpose of receptors specifically present on both neutrophils and endothelial cells (Zenaro et al., 2015), (de Oliveira et al., 2016). Zhang *et al* developed PLGA wrapped neutrophil membrane that retained the external protein make up of neutrophils. These neutrophils-coated NPs can provide cartilage protection, target into cartilages and inhibit synovial fluid inflammation resulting in improving condition of arthritis. *In vitro* model, human arthritis model of mice was developed and the neutrophil-cloaked NP was successful in improving the condition.(He, Y. et al., 2018b)

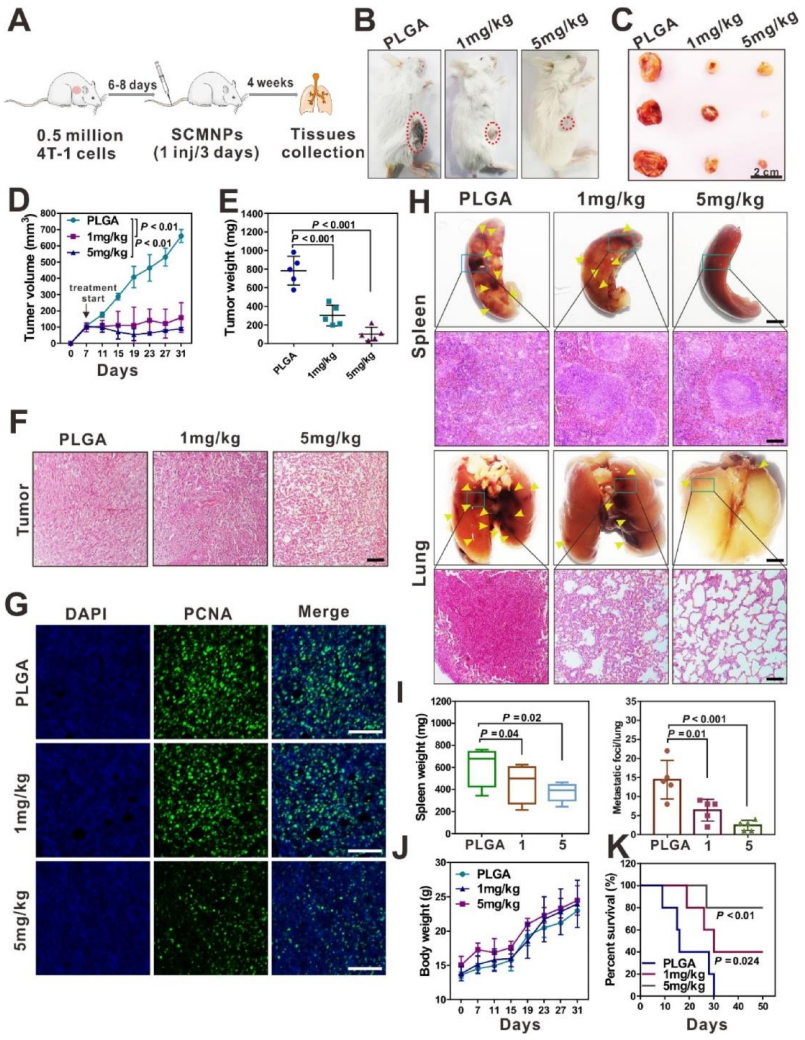


Fig.10. Results of in vivo experiment in mice conducted by Sun and group (2020). A. 4T1 injected to Balb/c mice for thrice a week for a month. B. Photographs taken of tumor (4T1 cells) bearing mice and of tumors (C) with bare PLGA NP administration, alongside. D and E represents the tumor growth curve with the administration of PLGA, 1 mg/kg and 5 mg/kg SMNPs, showing decrease in tumor volume. F. H and E staining results of tumor bearing mice with less injuroes observed for 5 mg/kg dose G. PCNA staining with anti-PCNA mAb for PLGA , 1 mg/kg and 5 mg/kg doses of SMNPs, PCNA that represents proliferative activity which is reduced in case of 5 mg/kg dose. H. External images of lung and spleen and corresponding H and E (Haematoxylin and eosin) stained images showing less metastatic nodules. I. Tumor nodule quantification and correlation with weight of lung and spleen. Body weight observed of all test groups during the span of 31 days period showing no much deviation. K. The survival curves of mice after treatment (Kaplan-Meier survival curve) for 50 days. (Sun

et al., 2020) Adapted with permission from Sun et al. (2020). Elsevier, Copyright © 2020, Elsevier".

NK cells are the granulocytes and they target cancer cells by releasing perforins and granzymes (Suck et al., 2016), (Koch et al., 2013),(Maki et al., 2001). Pitchaimani *et al* developed " NKsome" developed by making DOTAP:DOPE:cholesterol liposome fused with NK cells NK-92 (Natural killer cells, a lymphocyte) encapsulating doxorubicin targeted for breast cancer therapy both under *in vitro* and *in vivo* conditions and the NKsome was retained in the blood for 18 h exhibiting its effect (Pitchaimani et al., 2018). Han *et al* developed a T cell mimicking NP by making PLGA- lipid NPs and labelled with indocyanine green, coated with N3 labeled T cell membrane that can effectively target Burkitt's lymphoma. A novel bicyclo [6.1.0] nonyne (BCN) modified unnatural sugars (Ac4ManN- BCN), that are artificially introduced to cancer cells, mediating dual targeting. IV administration of the nanoformulation was given followed by laser irradiation for 5 min. The N3TINPs had highest tumor ablation ability reaching to 53°C, as compared to 41 and 36 °C for ICGNPs and PBS, that was inefficient in ablation of tumors (Han, Y. et al., 2019). Similarly, in another study by Zhang *et al*, T cell coated PLGA NPs for targeting gastric cancer and local low dose irradiation being employed as chemoattractant for the sole purpose of targeting. There was decrease in macrophage uptake of the NP by 23.99% and paclitaxel loaded Tcell coated NPs could decrease the tumor volume by 56.68% in Balb/c nude mice. It was also proved that the unharmed LDI can increase the expression profile of adhesion molecules on the tumor vessels that can selectively endocytose the paclitaxel loaded T cell coated NPs by homotypic targeting (Zhang et al., 2017)

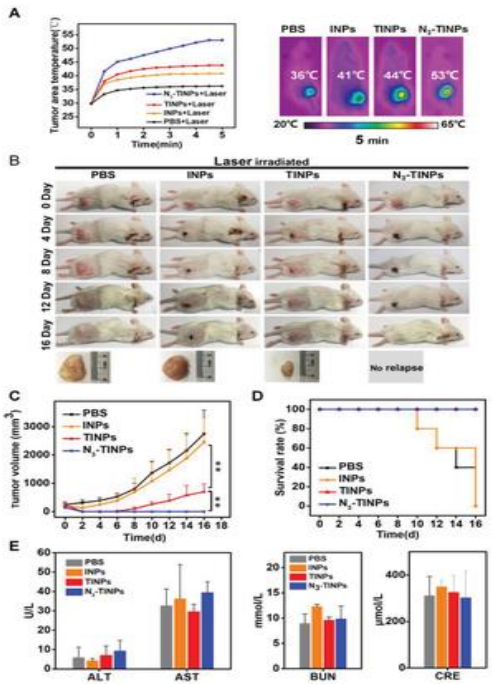


Fig.11. *In vivo* photothermal therapy and efficiency of dual targeted N3 TINPs. A. Result showing the temperature curve and IR thermal images of mice injected with tumor cells , showing that N3 TINPs could reach to 53 °C that can kill tumor cells, B. Results of mice with Raji tumors and the ex vivo tumors, showing a decrease in tumor size after administration of laser irradiation with N3 TINPs, C. Raji tumor growth curves treated with different groups of NPs D. Survival rates of tumor-injected mice showing N3 TINPs and TINPs had 100 % survivability after 16 day treatment. E. Blood biochemistry tests of important metabolic markers indicating there was no significant side effects.(Han, Y. et al., 2019). Adapted with permission from Han et al .(2019).

Therefore, it will be better to infer that WBC coated NPs can easily target tumors and excel be it in drug delivery and PTT, as seen in the above case studies. The intrinsic kicking capacities of macrophages to evading immune system, it is a boon in translational science to coat WBC with NP for mediating various therapeutic implications.

5.3. Platelet membrane coated Nanoparticles (PMNPs)

Platelets originate from megakaryocyte progenitor cells and have a life span of 10 days with participation in various immunological processes and metastasis model (Thon and Italiano, 2012).

Platelets are also devoid of cell nucleus, like RBCs and share the same protocol of extraction of cell membranes(Yao et al., 2019).Platelet membrane contains proteins that includes CD47 (for macrophage evasion), CD44 and p-selectin as p-selectin have high affinity to circulating tumor cells by binding to adhesion molecules such as CD44, CD 55/59(evading complement mediated immune activation) (Wang, H. et al., 2019), (Li, Z. et al., 2018), (Moghimi et al., 2016).Platelets have also been known to induce platelet aggregation that is induced by tumors that is dependent upon Gp (glycoprotein)IIb/IIIa receptors that can play key role in regulating angiogenesis. These various adhesive glycoprotein membrane proteins offer benefit of coating platelet membrane onto various inner core NPs, helping evade macrophage and better targeting ability. Wang *et al* designed a PLGA NP core taking emulsifier Vit-E-TPGS and conjugated it with chitosan (CS) to make the NP hydrophilic, encapsulating bufalin, an anticancer agent and coated the CS-PLGA with platelet membrane (PLTM), abiding by the hypothesis that platelet membrane coating with NP adhere to CD44 + tumor cells via p-selectin on it's own membrane (Fig. 10) (Wang, H. et al., 2019). *In vitro* cytotoxicity revealed that the bare CS-PLGA NPs and PLTM-PLGA-CS NPs did not have any cytotoxicity upto 500µg/ml. However, the cell viability declines to 17.9% with 20 µg/ml Bufalin inside PLTM-CS-PLGA NPs and the cellular uptake was 7.4 fold greater than PLGA-CS NPs. Increased strong fluorescence signals were observed for PTM-PLGA-CS NPs after 6h and even after 24 h post injection in *in vitro* mice model, suggesting good targeting ability of the biomimetic NPs.

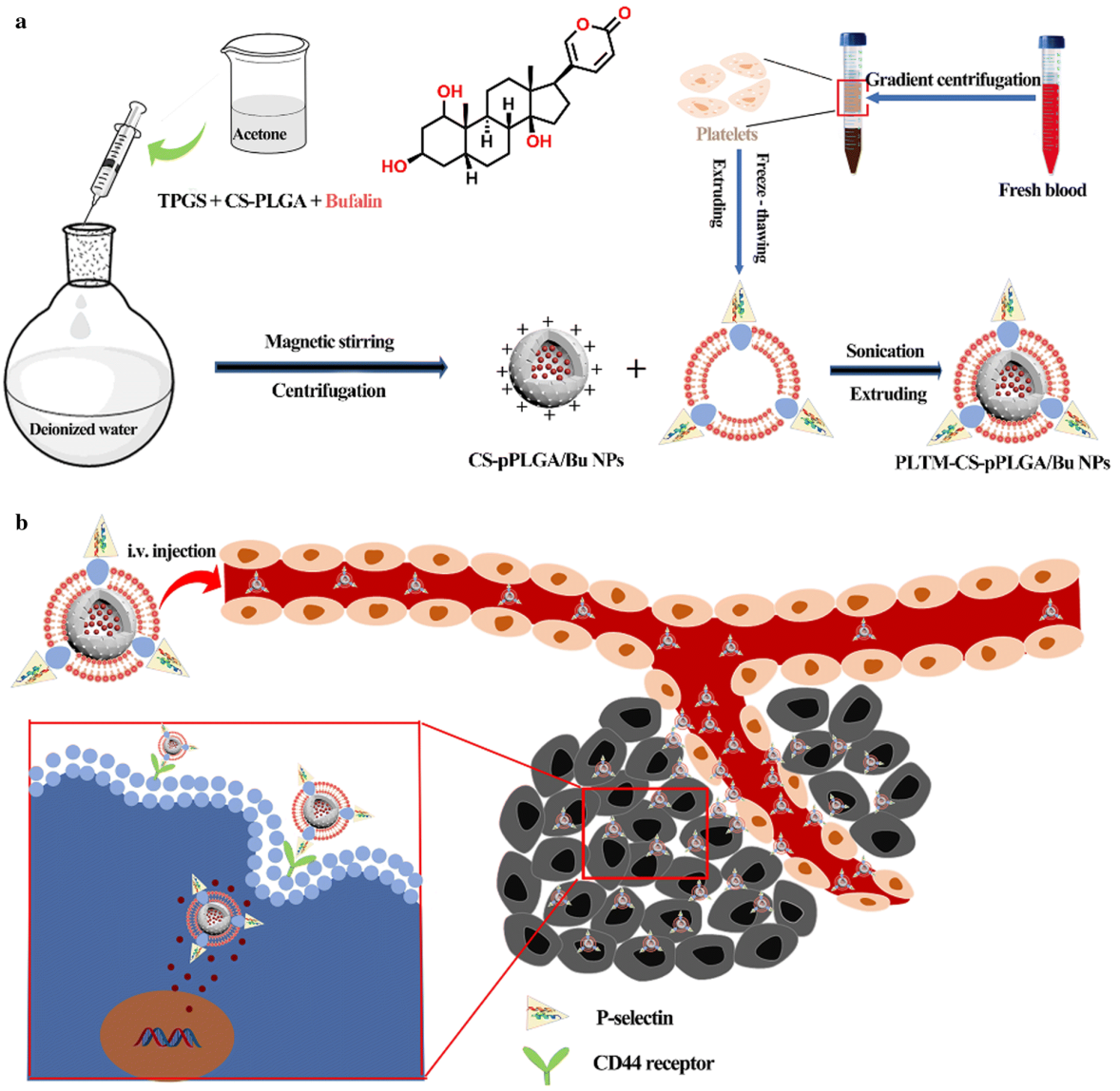


Fig.12. a. Preparation technique of Platelet membrane (PLTM)coated CS-PLGA NPs@ Bufalin by nanoprecipitation method with Vit E-TPGS. b. Binding of p-selectin to CD44 + Hep 22 tumor cells (hepatocellular carcinoma), leading to enhanced accumulation of Platelet membrane coated CS-PLGA NPs@ Bufalin into tumor cells(Wang, H. et al., 2019). Adapted with permission from Wang et al.(2019). This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

It is well known that platelets can bind to various molecules present on atherosclerotic plaques to recruit monocytes and T cells to the site of inflammation and thus, sensitize the plaques(Gawaz et al., 2008). This hinted Song and co workers in the year 2018 to develop a platelet membrane cloaked PLGA NP (PNPs) encapsulating Rapamycin, which is a potent immunosuppressor against Atherosclerosis. The binding of PNPs to sclerosis was done by taking collagen, fibrin and Vwf (a glycoprotein). For *in vitro* experiments, Apolipoprotein E deficient, (Apo E -/- mice) has been taken since, Apo E protein is responsible for transporting LDL (low density lipoprotein) particles and cholesterol efflux from macrophages regulating immune responses (Greenow et al., 2005). The PNPs could effectively bind to collagen and fibrin clots with 8.34 and 9.61 fold respectively as compared to NPs. As macrophages i.e. RAW 264.7 internalize the LDL and convert to foam cells in aorta to form atherosclerotic lesions, it was necessary to see the uptake profile of PNPs and Rap-PNPs with macrophages which showed that in Apo E -/- mice, there was 4.98 fold greater radiance energy than bare NPs depicting higher accumulation of PLTM @PLGA NPs in atherosclerotic plaques. Sudan red stained Apo E -/- mice showed reduced lesions in the plaque area after Rap-PNPs therapy. H and E staining showed that with Rap-PNPs, there was no injury in heart, liver, lungs, brain and spleen. Blood biochemistry analysis revealed that there was no harm to hepatic and kidney functions after treatment. (Song et al., 2019). Similarly, He *et al* encapsulated an immunosuppressive drug named, FK506 within platelet camouflaged PLGA NPs for targeting Rheumatoid Arthritis (RA). It was found that the targeting ability of platelets NPs had enhanced targeting ability to inflamed endothelium and high accumulation in joints of collagen induced arthritis (CIA) model of mice utilizing the P-selection and GVPI receptors(He, Y. et al., 2018a). Wu *et al* developed polypyrrole nanoparticles (acting as photothermal agents, with strong conductivity) modified with platelet membrane for encapsulating doxorubicin followed by laser irradiation of 808 nm to treat hepatocellular carcinoma in an orthotopic mice model(Wu, L. et al., 2020),(Zhu, Y.D. et al., 2016). This new biomimetic NP not only assisted in targeting HCC but also ablate tumor cells after laser irradiation, high temperature ruptured the platelet membrane and triggered drug release at the tumor site effectively, thus acting as a better reliable model for anticancer therapy.

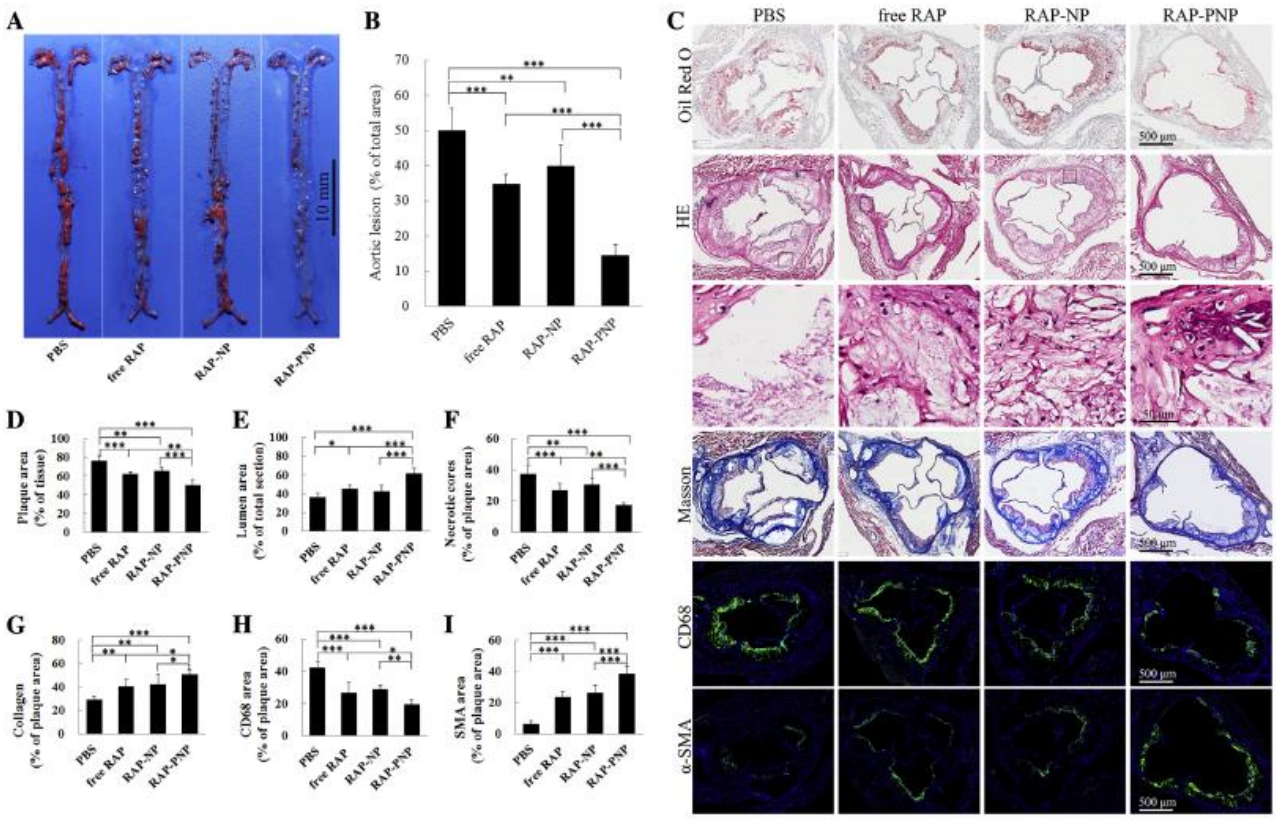


Fig.13. *In vivo* anti atherosclerosis activity by Rap-PNP. A. Sudan red stained (front-facing) images of aortas from different groups showing less lesions in the Rap-PNP group. B. Aortic lesions quantified in comparison to total luminal area, with minimum lesions in Rap-PNPs treated group. C. Cross section of aortic tissues;stained with oil red O dye, hematoxylin-eosin (H&E) and Masson's trichrome while density of macrophages being evaluated by IHC (staining antibody with anti-CD68 antibody, that recognizes macrophages) and for abundance of smooth muscle cells (SMCs), the sections were stained with anti-α-SMA antibody. Rap-PNPs group showed improving condition of anti-sclerotic lesions as evidenced by less LDL, HE stain showed less acellular cores and cholesterol clefts as compared to other groups (images in the third rows show magnified plaques as informed by the author (scale bar = 50 μm). Masson's trichome staining showed less complication of necrosis in Rap-PNP group, relative less uptake by macrophages in Rap-PNPs group as shown by less staining by anti-CD68 antibody, anti-α-SMA antibody showed there was increasing smooth muscles actin positive area with Rap-PNPs treatment. Quantitative analysis of (D) plaque area decreasing in treated group, (E) lumen area, (F) reducing necrotic cores (G) comparative reduced collagen content of Rap-PNPs treated group

(H) reduced macrophage area i.e. decrease in foam cells and (I) increase in SMCs with all groups. (Song et al., 2019) Adapted with permission from Song et al (2019). Elsevier, 2019.

Platelets have low immunogenicity profile and high biocompatibility and can serve as a better choice of stealth or biomimicking material with all the self leveraged proteins on it to target to areas of injuries and inflammation, thus act as a good coating around NPs for enhanced therapeutic grounds.

5.4. Cancer cell membrane coated Nanoparticles (CCMNPs)

Tumor cells have this unique property of escaping immune cells (NKcells, macrophage/monocytes) and does not induce the immune orchestra. The cancer cell membrane contains certain adhesion glycoproteins that act as anchor proteins and also for attaching cell to cell. The proteins are: N-cadherin, Epcam, Carcinoembryogenic antigen, Galectin-3 (Osta et al., 2004),(Zhu, J.Y. et al., 2016), (Fang, R. H. et al., 2014), (Fang et al., 2018), (Hu et al., 2015). The proteins mediate homotypic binding and can be endocytosed by the "like" cell expressing similar proteins on the membrane, thus can be coated onto nanoparticle cores and be a better option than RBCs and WBCs for antitumor drug delivery to the tumor sites as the cancer cell as it can hide well in the body system and target to the desired site. Fang *et al* in 2014 developed a PLGA nanoparticle as inner core and fused it with B16−F10 mouse melanoma cell membrane to get CCMNPs, which had better uptake profile than RBCNPs when incubated with MDA-MB-435 cells . Cancer cell membrane can also be functionalized on NP core for cancer antigens for immunotherapy as the low immunogenic antigens on the membrane boost the immune response to an extent that can induce cytotoxic T cells (Tc cells), dendritic cells and also interferons/cytokines, without much affecting the physicochemical characteristics of the NPs. (Fang, R. H. et al., 2014) Various works have been done by scientists to develop cancer cell membrane camouflaged NPs that have done wonders when it comes to delivering drugs and imaging agents utilizing homotypic binding to adhesive molecules on cancer cell membrane. The CCMNPS has also brought enormous success in immunotherapy (Li, R. et al., 2018), (Kroll et al., 2017) .

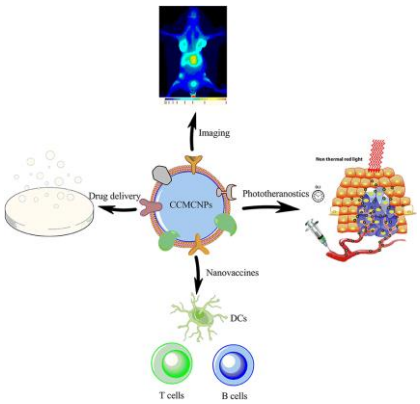


Fig.14. A cartoon illustration of cancer cell membrane coated NPs (CCMNPs) harnessed for cancer immunotherapy via tumor associated antigens mediated immune response, drug delivery, imaging and targeting due to homotypic binding(Jin and Bhujwalla, 2019) . Adapted with permission from Jin et al.(2019). "Distributed under the terms of the Creative Commons Attribution License (CC BY), Copyright © 2020 Jin and Bhujwalla".

Nie *et al* in 2020 developed a mesoporous silica NP core designed with PEGylated liposome yolk and cancer cell membrane coating that encapsulated Dox and the PARP inhibitor mefuparib hydrochloride (MPH) (a DNA repair inhibitor that act synergistically with Dox and have an IC50 of 50 μM)(Nie, D. et al., 2020). First, mesoporous silica NP was wrapped with PEGylated liposome to produce the lipid bilayer membrane coated mesoporous silica NP designated as MSN (LM), and again cloaked with MCF-7cell membrane (CCM) or 1, 2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) liposome to produce yolk-shell-structured NPs, which were symbolized as CCM@LM and L@LM, respectively.

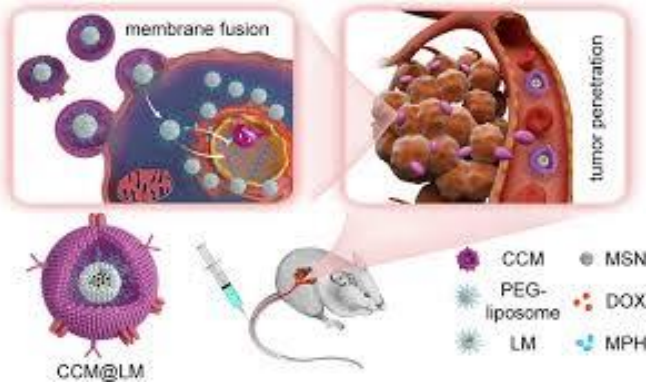


Fig. 15. Schematic of the work done by Nie and co workers showing that yolk shell structure of CCM@LM with Dox and MPH leads to enhanced tumor penetration and improved anticancer therapy(Nie, D. et al., 2020). Adapted with permission from Nie et al.(2020). *Copyright © 2020, American Chemical Society*

The NP cell uptake with MCF-7 had the highest MFI (mean fluorescent intensity) than other cell lines suggesting good homotypic binding. CCM@LM also showed little or negligible protein adsorption than other groups (LM, L@LM, MSN (LM) with no changes in physicochemical properties like charge and size. Uptake by J774A.1 cells was also evaluated to check NP uptake by macrophages to see immune evasion property, which showed that CCM@LM could evade immune system as it was not uptaken by J774A.1 cells. It was also shown that CCM@LM penetrated to depths at larger extent due to facilitated cellular internalization in a multicellular spheroids (3D) model. It was shown that CCM@LM with Dox and PARPi (MPH) (1 mg/kg) exhibited 95% tumor inhibiting ability showing its ability to penetrate into tumors as compared to other groups. Similarly, Zhang *et al* worked on rod shaped MSNs and spherical MSNs wrapped by CCM derived from BxPC-3 cells with Dox as antitumor agent and it was inferred that the rod MSNs wrapped by CCM escape macrophage uptake and endocytose into tumor cells by caveolin-mediated endocytosis. In hybid tumor bearing mice (BxPC-3) & pancreatic stellate cell (HPSC), the rod MSNs wrapped by CCM had 8.2 fold higher ECM penetration than the spherical MSNs wrapped by CCM counterparts, leading to upgraded antitumor potential(Zhang, W. et al., 2019). Zhang and co authors designed a nucleic acid (small interfering RNA (siRNA E7) (targeting to Plk1 gene) delivery system by coating cancer cell membrane onto poly(β-amino ester) (PBAE) NPs inducing apoptosis mediated cell death (Zhang et al., 2020). In another study, Xu *et al*, designed PLGA NP core camouflaged with HeLa cell membrane and loaded with siRNA/ Paclitaxel (PTX), thus a more biocompatible dual-drug delivery system (Si/PNPs@HeLa). To confirm the membranes present on the right side out conformation, coomassie blue staining (to visualize the protein bands) and immunostaining for epithelial cell adhesion molecule (EpCAM) and galectin-3 was done. Anti CD47 was also checked to see the presence of CD47 marker, which is highly expressed in cancer cells for evading immune response. Cellular uptake of Si/PNPs@HeLa by RAW264.7 cells showed that median fluorescence intensity is lower than Cy5-SiNPs, which depicted that there is immune evasion. Similarly, Si/PNPs@HeLa showed enhanced anti tumor ability. In *ex vivo* condition, tumor accumulation of DiR-NPs@HeLa was found to be higher by 3 folds than that of DiR-NPs. There was much lower accumulation of

Si/PNPs@HeLa in organs like liver and spleen. The Si/PNPs@HeLa had 83.6% tumor inhibiting capacity as compared to other groups (Xu et al., 2020).

Photothermal agents coupled to chemotherapy in CCMNPs is quite popular to target cancer (Li, R. et al., 2018), (Zhang et al., 2018) (Chen, Z. et al., 2016), however recently there has been a buzz about PDT (Photodynamic Therapy implies exposure of a photosensitizer compound along with light to destroy cancer cells) combined with starvation therapy. i.e. glucose oxidase when delivered to tumors transforms glucose to gluconic acid and H2O2, leading to starvation of tumor cells. A MnO2 nanoreactor encapsulated with a PS and coated with glucose oxidase and camouflaged with B16-F10 melanoma cells. Upon delivery to tumor region by homophilic targeting, the nanoreactors irradiated will generate singlet oxygen that reduces the tumor (Pan et al., 2019). Rao *et al* developed gelatin NPs coated with patient derived cell HNSCC loaded with cisplatin that reduced tumor to a considerable amount and has the potential to become a personalized therapy in future. Immunotherapy being a recent subject has also reached heights for reducing metastasis. (Rao et al., 2019c). Jin *et al*, designed PLGA core coated with human CCM fractions to induce an immune response and inhibit cell migration. In nude Balb/c mice, there was high number of CD8+ and CD4+ T cells in the lymph node region and spleen of CCMF-PLGA NPs treated mice. Also, there was cytokine elicitation (interferon-γ) thus showing a promising future in immunotherapy.(Jin et al., 2019)

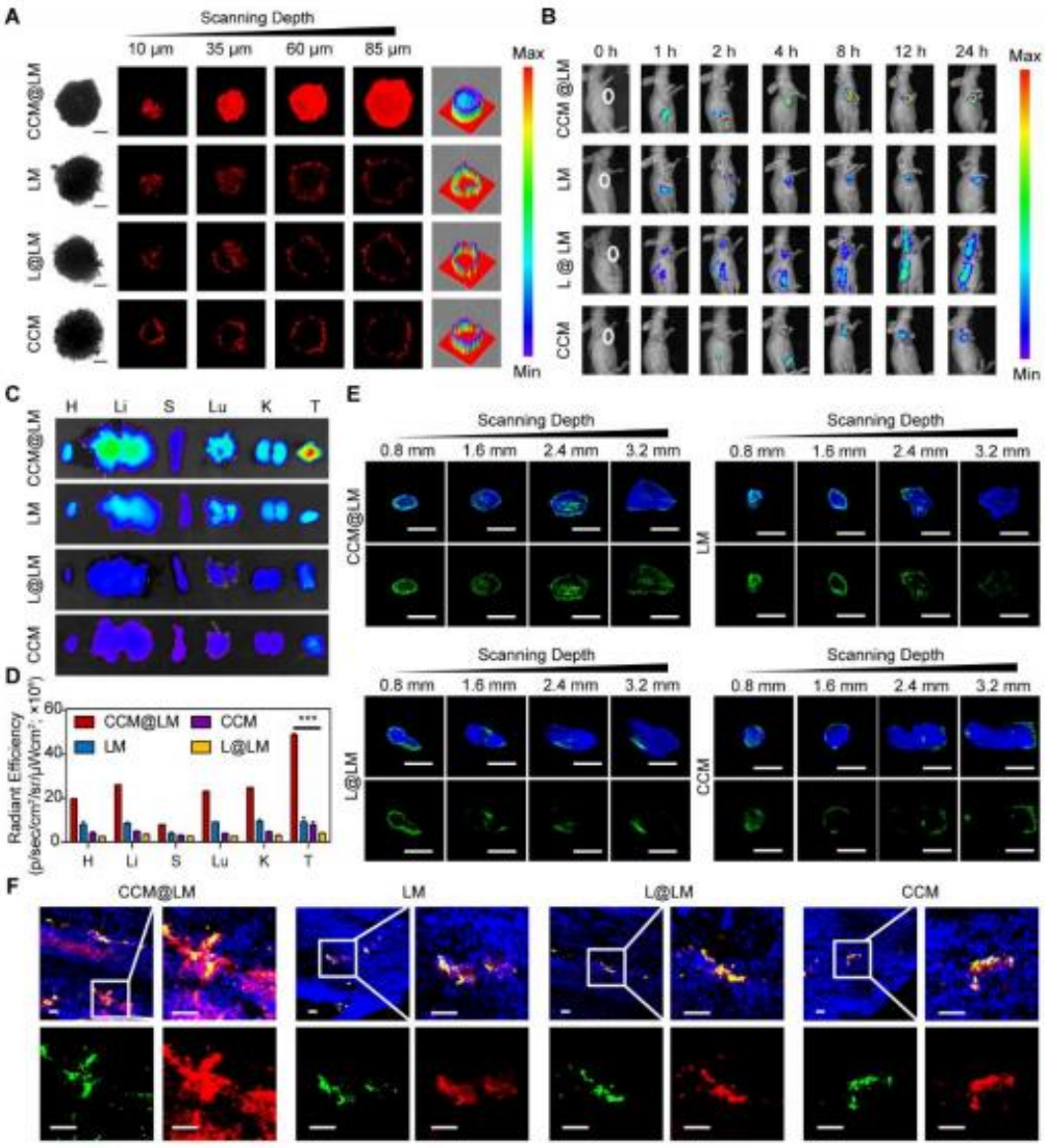


Fig.16. Results of tumor penetration to support the hypothesis of homophilic tumor targeting A. *In vitro* confocal images of DiI labeled NPs colocalization to MCF-7 multicellular spheroids, showing enhanced penetaration ability of CCM@LM, B. Real time NIR in vivo images of IR783 labeled NPs in tumor bearing mice showing that CCM@LM penetrated to tumor area within 4h post injection, as compared to other groups, C. Ex vivo results showing pictures of tumor tissue (T) and other vital organs (H: heart; Li: liver; S: spleen; Lu: lungs; K: kidneys) to show that CCM@LM had enhanced penetration to tumor tissues than other organs , D. Semi quantitative MFI (mean fluorescent intensity) to show the accumulation of different groups of NPs in different organs post 24 h injection, E. CLSM images of FITC (green) labeled NPs and DAPI

stained blue, to show tumor penetration ability of CCM@LM NPs in MCF-tumors. F. DiI labeled NPs in MCF-7 tumor xenograft sections after 8h of tail vein injection, the blood vessels being stained with anti CD-31 antibody. White outlines show blood vessels. CCM@LM could extensively penetrate to tumor area crossing the blood vessel barrier while other NPs hardly can cross the endothelium being near the blood vessels. (Nie, D. et al., 2020) Adapted with permission from Nie et al. (2020). *Copyright © 2020, American Chemical Society*.

Summarizing, it can be said that the homotypic targeting efficiency of cancer cells can be put in various research lines to generate innumerable anti tumor ventures, combining the chemotherapy, PDT and starvation therapy or immunotherapy.

5.5. Stem cell membrane coated Nanoparticles (SCMNPs)

Stem cells or mesenchymal stem cells have the unique property of long term proliferation. MSCs can circulate in the bloodstream for a considerable duration, can evade immune system and contains ligands that can target the tumor cells (Wu et al., 2019), (Yao et al., 2019).The cancer cell membrane coated NPs offered huge advantages and this paved way to extend the research on MSCs coated NPs for targeting inflamed, tumor prone regions, and metastatic models. MSCs can be isolated easily and can be produced from variety of tissue types generating a wide level of possibility for therapeutic applications(Uccelli et al., 2008), (Majumdar et al., 2003). Gao *et al* generated stem cell membrane vesicles and co extruded the vesicles with gelatin nanogels via a 400 nm polycarbonate membrane to form stem cell coated gelatin nanogels encapsulating hydrochloride Dox (SCMGs-Dox). Bare NPs had no cytotoxicity upto 400μg/ml upto 24h and SCMGs release the drug Dox in acidic condition (at lopw pH). MTT of SCMGs-DOX, gelatin NPs-DOX, or free DOX at concentrations of 0.01–100 μg/ml was done and it was shown that IC50 of SCMGs-DOX came out to be 0.63 μg /ml, much lower than that of gelatin NPs-DOX 2.55 μg /ml. Approximately 100% uptake of SCMGs-DOX by HeLa cells was seen and cy7-SCMGs accumulated to a large extent in tumor area as seen by fluorescence intensity. Also, spleen, kidney, liver, and lung, contained low number of SCMGs. PBS, gelatin NPs, free DOX, gelatin NPs-DOX, and SCMGs-DOX was administered intravenously and the SCMGs treated group displayed enhanced progression in reduced tumor growth when compared to the control groups after a duration of 15 days.(Gao, C. et al., 2016)

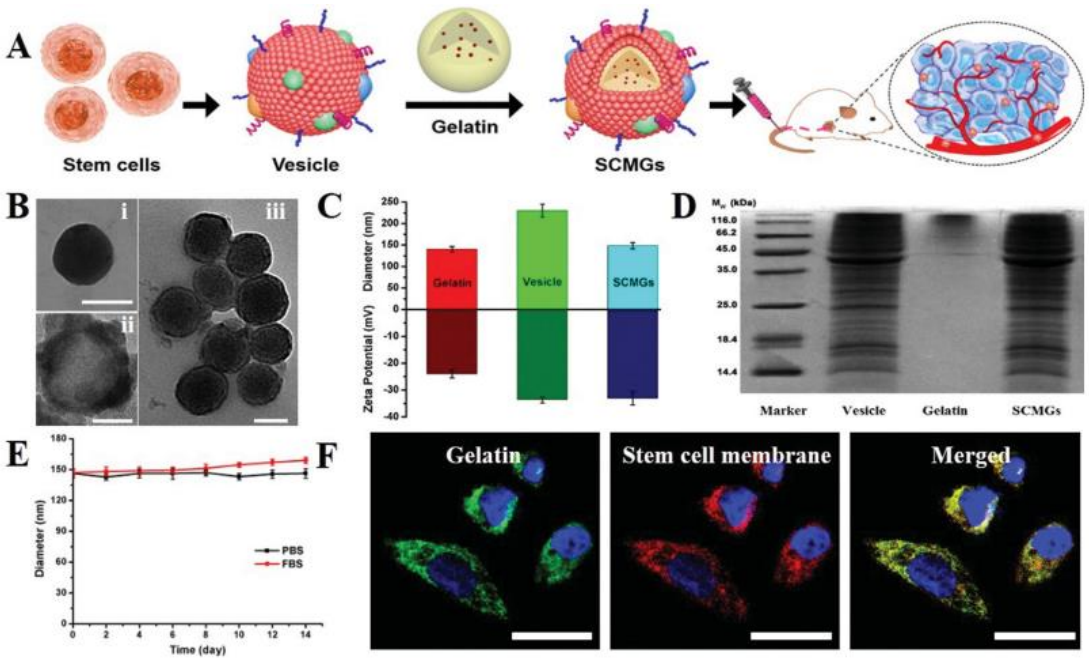


Fig.17. A. Schematic showing preparation of SCMGs by co extrusion method and *in vivo* treatment to treat tumor. B. Representative TEM images of i. void gelatin nanogels ii.vesicle of stem cell and iii. stem cell coated with gelatin nanogel. C. DLS data showing size and zeta potential of gelatin nanogel, stem cell vesicle and stem cell coated gelatin nanogel. D. A SDS – PAGE showing that the SCMGs retained the protein make up of stem cell membranes confirming the right side out conformation with no proteins on only gelatin nanogels. E. The SCMGs were suspended in PBS and FBS over a period of 2 weeks and minimal reduction in size was noted. F. FITC (green) labeled gelatin cores and cell membranes labeled with DiD (red) were incubated (co-culture) with HeLa cells for 0.5 h to see the unification of the core shell structure was observed when merged images were seen. (Gao, C. et al., 2016). Adapted with permission from Gao et al.(2016).

Similarly, Mu *et al* worked on polydopamine coated Fe3O4 nanoparticles that is again modified with mesenchymal stem cell membrane encapsulating siRNA against Plk1 gene (MSC -Fe3O4-PDA NPs-Plk1) that would lead to apoptosis of DU145 cells (human prostate cancer cell line). All the nanoparticle groups were tested both in cell culture and in mice model. It was found that the photothermal conversion energy of Fe3O4@PDA was almost similar with MSC -Fe3O4-PDA NPs-Plk1 due to MSC coating as the lipid bilayer of the stem cell membrane absorbed some heat, still enough to bring ablation. The T2-weighted relaxation rate value (r2) is basically accounted for when

doing an MRI scanning. T2 is the duration the signal takes to decay. An increased r2 value signifies increased accumulation of iron, thus here it can be interpreted as higher concentration of MSC -Fe3O4-PDA NPs-Plk1.The r2 value suggested efficient MRI ability. In *in-vitro* system, MSC -Fe3O4-PDA NPs-Plk1 had no considerable cytotoxicity at or beyond 200µg/ml against normal 293t cells. 90% cell death was seen when DU145 cells were treated with Fe3O4-PDA or MSC -Fe3O4-PDA-NPs Plk1 under laser irradiation for 5 minutes straight. No such dramatic decrease in cell viability was seen for NIR laser without the aid of NPs. The MSC-Fe3O4-PDA NPs-Plk1 had good biocompatibility with no hemolysis issue and was found to have higher tumor accumulation than the other groups due to MSC coating. After a 15 day treatment of Fe3O4@PDA-siRNA@MSCs NPs with laser irradiation, the tumor inhibition efficiency reached 60% with no major inflammation or necrosis in major organs, as evidenced by HE staining(Mu et al., 2018a)

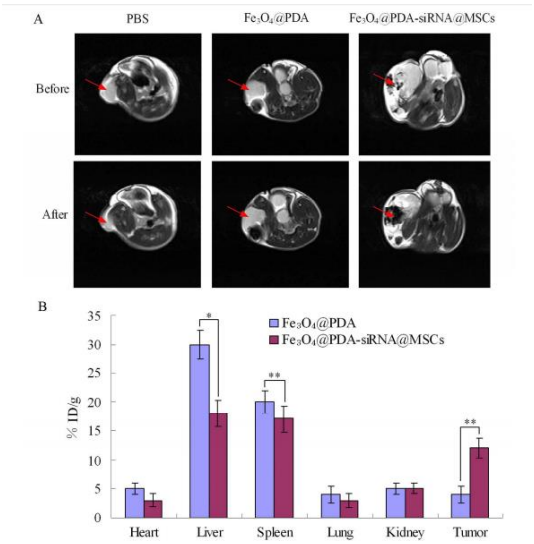


Fig.18. In vivo tumor diagnosis of BALB/c nude mice injected with DU145 cells (Mu *et al*., 2018) . A. T2-weighted MR images of NPs treated mice, darkening effect of the tumor area showing that the MSC -Fe3O4-PDA NPs-Plk1 can be good targeting and MRI probe in *in vivo*. B. ICP-AES (Inductively coupled plasma atomic emission spectroscopy) analysis of the MSC -Fe3O4-PDA NPs-Plk1 NPs showing that the quantity of stem cell modified NPs had higher accumulation in tumor tissue over other organs.(Mu et al., 2018a). Adapted with permission from Mu et al. (2018). *Copyright © 2018, American Chemical Society*.

In other study conducted by Bose *et al*., the authors developed a stem cell membrane functionalized with CXCR4 antibody coated PLGA NPs to target ischemic tissue. The stem cell

membrane was derived from human adipose-derived stem cell. Coating with MSC led to reduced cell uptake by human (THP-1) and mice (J774) macrophages with the ability to cross the endothelial barrier, the NPs retained in ischemic tissue (endothelium after a 14 day treatment.(Bose et al., 2018) Gao and co workers, camouflaged MSCs on mesoporous silica NPs and encapsulated β-NaYF4:Yb3+, Er 3+ up-conversion NPs (photosensitizers) that were loaded with ZnPC and MC50. The NPs followed by laser irradiation at 980nm could effectively bring the anti tumor activity. As exemplified by all these case studies, it is clear that MSC coated NPs can effectively circulate for an extended period of time and evade immune system thus compensating for tumor cell coated NPs with provision for crossing the endothelial barrier by functionalizing it with required ligands. (Gao, Changyong et al., 2016)

5.6. Others

Besides the popular choice of cell membranes, some other unconventional options have also been explored to coat nanomaterials. For instance, activated fibroblasts that are involved in metastasis, cancer growth and present in tumor stroma have been used to coat semiconducting polymer NPs (SPN) to target tumor surrounding activated fibroblasts (AF). The activated fibroblast coated SPN AF-SPN had a high accumulation in the tumor area enabling PDT in the precise tissue where intended (Erez et al., 2010), (Li, J. et al., 2018). Beta cells need interactions for their growth and recently, authors have successfully designed a scaffold made up of PEG hydrogels that helped in the proliferation of the MIN6 cells. The PEG hydrogels when decorated with EphA5-Fc receptor and ephrinA5-Fc ligands and cell adhesive peptides, led to enhanced survivability and growth function(Lin and Anseth, 2011). Polycaprolactone nanofibers have also been used to promote the growth and glucose dependent insulin secretion of the seeded beta cells (Chen, W. et al., 2016). Cell derived vesicles and exosomes can also be used as cargo for delivering therapeutics to targeted site(Li, S.P. et al., 2018),(Mentkowski et al., 2018). Apart from this, bacterial cell membranes have been also explored as bacterial cell contains peptide immunogens or epitopes that can elicit immune response against a pathogen (basically acting as a subunit vaccine with nanoparticles for imparting stability and extended circulation inside body). By cloaking bacterial cell membrane onto nanocores, one can target antigen presenting cells, T cells (cell mediated immunity) which can stimulate the humoral immunity (B cells for antibodies) to fight against infections(Gao et al., 2015), (Angsantikul et al., 2015), (Zaman and Toth, 2013),(Langemann et al., 2010). Zhang's team developed *Escherichia*

coli outer membrane vesicle coated onto small Au NPs to elicit an immune response (Dendritic cells, INF-γ, IL-17) with high durability and avidity than naked outer membrane vesicles(Zhang, Y. et al., 2019). Recently, Gao and co authors treated *Staphylococcus aureus* bacterimia by coating the bacterial outer membrane to PLGA NP (NP@ EV-EV for extracellular vesicles. The NP@EV accumulated by *S.aureus* infected macrophages whereas the controls (PEGylated liposome and E. coli OMV). This mode of active targeting achieved success both in *in vitro* and *in-vivo* systems (bacteremia bearing mice model). NP@EV accumulated higher in liver, spleen, heart and lungs, in comparision to PEGylated liposome and E. coli OMV and more efficiently in kidney and lungs bearing metastatic *S. aureus* bacterial burden.(Gao et al., 2019)Apart from the individual cell membranes, hybrid cell membrane coated nanoparticles are also in trend now. Recently, Liu and co workers developed a hybrid (RBCs and Platelet) membrane coated polypyrrole (PPy) NPs for rendering the NPs immune evasion and with tumor targeting ability. The PPy@(R-P) NPs followed by photothermal ablation in mice leads to thrombocytopenia in the blood vessels that recruits the PPy(R-P) NPs to the injured site as there was excess of platelet membranes in coating as a result of which potent antitumor ability was seen. The hybrid NPs were prepared by incubation and co extrusion. The RBC membrane was mixed to platelet membrane by co-incubation (individually isolated) at weight ratios of RBC membrane to platelet membrane protein of 1:1, 2:1 and 1:2 followed by sonication at 4 °C for 3 minute duration to obtain the RBC-Platelet membranes. After the hybrid membrane was synthesized, it was used to coat on the PPy NPs by co extrusion. The cell viability of HCT116 cells (human colon cancer cell line) was only 20%, when the cells were incubated with PPy NPs followed by irradiation for 180 s. PPy@PLT NPs group displayed short durability in blood 24 and 48 h after intravenous injection, respectively which shows that the RBC coating helped in increasing the durability of the NPs in blood. (Liu, Y. et al., 2018)

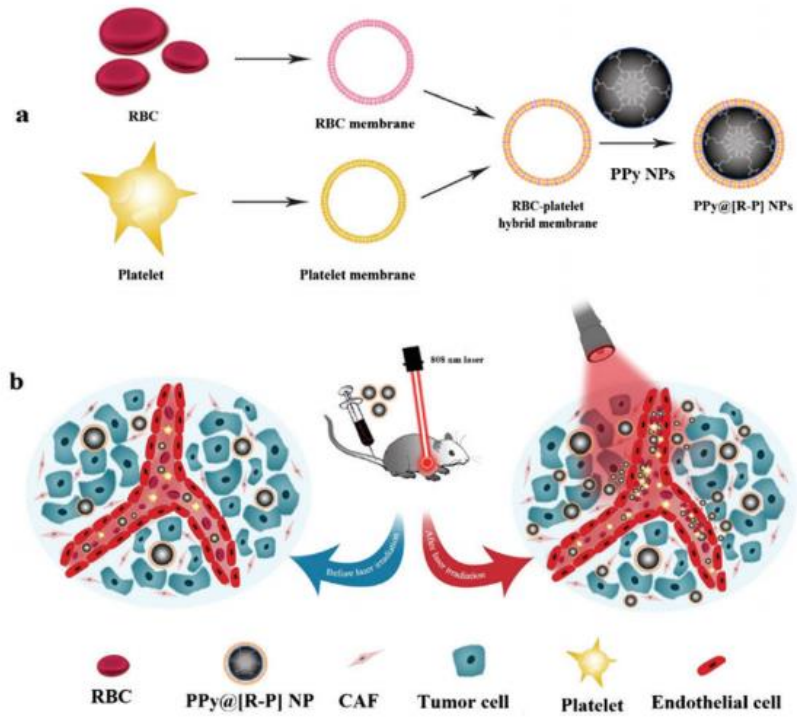


Fig 19. a. A diagrammatic representation of the fusion of RBC-Platelet membranes and coated on PPy NPs to form RBC-platelet hybrid NPs that will have the dual property of self targeting (platelet) and long circulation via the CD47/SIRP-a pathway (RBC). b. The hybrid PPy NPs when administered by tail vein injection, injury of tumor vessels occurs that recruits the NPs onto the thrombosis site due to platelet membrane coating. Tumor targeted NPs then upon NIR laser treatment ablate tumor (photothermal effect)(Liu, Y. et al., 2018) "Reproduced from Ref. 74 with permission from the Royal society of Chemistry".

Similarly, Jiang and co workers in 2018 worked on RBC –MCF-7 (1:1 in ratio) hybrid melanin NPs to target melanoma. It was proved that the melanin NPs coated with (RBC-MCF) had a better targeting ability than the uncoated and the other cell membrane coated counterparts. In mice model, upon administration of melanin (RBC-M) NPs with laser irradiation, the temperature rose to 54°C within 10 mins and there was 100% tumor inhibition and enhanced targeted tumor destruction as evidenced by H and E staining and TUNEL assay (Jiang et al., 2019). He *et al* encapsulated PTX in liposome coated with both leukocyte (J774A.1) and tumor cell (HN12). (He, H. et al., 2018). Rao and team developed platelet and WBC fused cell membranes and coated onto immunomagnetic beads that specifically binds to CTCs (circulating tumor cells) and reduce homotypic binding to WBCs helps in

isolation of CTCs with 66.53% to 96% when compared to commercial immunobead kits. (Rao et al., 2018)

It is now well imperative that cell membrane coating approach has enormously benefitted the translational background due to its versatility of various cell functions that can be harnessed to different sources of nanoparticle cores. Not only individual but hybrid cell membrane fragments have been now explored for dual advantage and making the most of it, one can take the advantage of both the cells used. Nevertheless, drug delivery to targeted sites, imaging, photothermal ablation therapy, sonotherapy, starvation therapy all can be explored very well while using diverse field of cell membrane coatings.

6. Advances and limitations

6.1. Advances

Cell membrane coating technology is a boon to researchers being a conglomeration of natural and synthetic entities. Most of the cell-based nanoparticles-targeting tumor is in the clinical phase due to the success in achieving biocompatibility. Model drugs such as doxorubicin, cisplatin, paclitaxel have undoubtedly therapeutic efficacy, however they have poor pharmacokinetics, biodistribution and a major problem of drug resistance. The natural targeting improves the accumulation of drug in the desired site, residing in circulation for a longer period without being recognized by mononuclear phagocytes. The membrane proteins already present on the cell membrane coated NPs provide all these advantages requiring minimum labour intensive work on the synthesis protocol in comparison to the conditions that are required while using immunonanoparticles. Each cell provides certain benefit that endows a CMCNP with added advantage, however they have certain limitations too. RBCs provide long circulation evading RES, however fail in active targeting, WBCs have homologous targeting ability, still it is specific to certain tumors, platelets survey for tumor sites and damage but it can activate the immune system, cancer cells have homologous adhesive ability/active tumor targeting but have shorter circulation time in blood, stem cells have tumor targeting ability but with low specificity and bacterial membrane have immune evoking property still the extraction of membrane becomes tedious as it requires peptidoglycan removal. According to the need, fusion of two membranes can be done effectively to form hybrid cells that can have therapeutic benefit of the two cells. In this section, certain recent patents that have been filed or granted on CMCNPs have been

listed in a tabular form (based on some studies from the review by Yao *et al*.,(Yao et al., 2019), google patents and Justia Patents)- data obtained on 04/05/2020) that encloses drug delivery, targeting, imaging , CTCs separation, profiling and characterizing unknown proteins binding to cell membrane coated nanoparticles.

Table 3. List of recent patents filed and granted related to CMCNPs.

Cell membrane type	**Patent number**	**Assignee**	**Patent theme**	**Patent filing year/status**
Red blood cell	US8329161B2	National Health Research Institutes	Red blood cell-derived vesicles as a nanoparticle drug delivery system(Huang, 2009)	Filed in 2009 Granted
Leukocyte	US20130071329A1	University of Texas system, Austin	Theranostic delivery systems with modified surfaces	Filed in 2011 Abandoned
Virus	DK2714017T3	University of California	Membrane-wrapped nanoparticles and method of use	Filed in 2011 Granted
Red blood - Platelet hybrid cell membranes	US7901674B2	The university of North Carolina at Chapel Hill, USA	Aldehyde fixed platelets with internalized paramagnetic or magnetic nanoparticles	Filed in 2011 Status pending
Red blood cell	W02013052167A2	The Regents of the University of California, Oakland, (USA)	Membrane encapsulated nanoparticles and method of use	Filed in 2012 Granted
Red blood cell	US20170367990A1	Cellics Therapeutics Incorportaion	Use of nanoparticles coated with RBC to enable blood transfusion	Filed on 2015 Granted
Red blood cell	US20170079909A1	The Regents of the University of California, Oakland, (USA)	Hydrogel toxin-absorbing or binding nanoparticles	Filed in 2015 Status pending

Red blood cell	US201702740591A1	The Regents of the University of California, Oakland, (USA)	Selfantigen displaying nanoparticles targeting auto-reactive immune factors and uses thereof(Zhang et al., 2016)	Filed in 2015 Status pending
Red blood cell	CN201610148434.5	East China Normal University, Shanghai, Putuo, China	Antibody nanoparticles encapsulated in erythrocyte membranes for delivery of antibody drugs and their preparation methods	Filed in 2016 Granted
Platelet	US20180169027A1	The Regents of the University of California, Oakland, (USA)	Treating Infection by a Platelet targeting microbe using Nanoparticles	Filed in 2016 Status pending
Cancer cell	WO2017030929A1	The John Hopkins university, Baltimore, Maryland	Decoy nanoparticles to disrupt cancer cell-stormal cell networks	Filed in 2016 Status pending
Extracellular Matrix	WO2017024193A1	The John Hopkins University, Baltimore, Maryland	Immunomodulatory Extracellular rmatrix nanoparticle	Filed in 2016 Status pending
Bacteria	US20180085320A1	The Regents of the University of California, Oakland, (USA)	Modulating antibacterial immunity via bacterial membrane coated nanoparticles(Gao et al., 2015)	Filed in 2016 Status pending

Cancer cell	CN201711431735.X	Zhengzhou University, Zhengzhou, Henan, China	Preparation and application of a hollow mesoporous TiO2 biomimetic drug complex coated with cancer cell membrane and loaded with Autophagy inhibitors	Filed in 2017 Status pending
Red blood cell	CN201811055247.8	Zhejiang Sci-Tech University , China	Preparation of biomimetic RBC membrane nanoparticles with targeting and photothermal integration	Filed in 2018 Status pending
Red blood cell	CN201810074719.8	Shanghai Jiao Tong university, Shanghai, China	Preparation and application of Berberine hydrochloride nanoparticles encapsulated by erythrocyte membrane	Filed in 2018 Status pending
Platelet	CN201810766716.0	China Pharmaceutical University. China	Preparation and application of bio-camouflaged targeted nano-delivery system for the treatmen ischemic stroke	Filed in 2018 Status pending
Neuron	US20200096503A1	The board of Trustees of the University of Alabama	Cell membrane coated Magnetic nanoparticles and assays for identification of transmembrane protein-binding compounds	Filed in 2019 Status pending

6.2. Existing limitations

Undoubtedly, CMCNPs bestows with innumerable therapeutic advantages along with it's biocompatibility. It avoids the usages of organic solvents, ligands, chemical conjugative moieties and highly reactive chemical agents for getting a targeted nanocomposite, is more eco-friendly, have a visible emission spectra and with excellent fluorescence properties that can be well suited for experiments(Li, R. et al., 2018). Although much has been achieved with cell membrane coated

nanoparticles, there still remains some room for challenges to deal with. The field is naïve and it is not fully grown to the translational level i.e. from lab to clinical trials. It needs good scalable and easy-to-manufacture practices.

Conclusion

Targeted drug delivery is an important and proven platform for combating toxicity of the drug and granting it with enhanced pharamacological behaviour. In recent times, various efforts have been made to make nanomaterials reach the diseased site effectively without compromising it's own half life in plasma. For prolonged circulation in blood and excellent targeting capabilities, cell membranes derived from different sources that included red blood cells, white blood cells, platelets, cancer cells, stem cells, bacterial, viral cells, etc have been coated onto synthetic nanoparticles. Cell membrane coated nanoparticles offers immense translational benefit as it retains both the property of cell membrane proteins and stability of nanoparticles. Cell membranes vesicle coated onto nanoparticles are with better stealth and targeting property. Recently, hybrid cell membrane coated nanoparticles are also being developed in order to compensate for any shortcoming of a single cell membrane coated nanomaterial to make it a versatile and multifunctional approach. It is inevitable that any new field suffers from lacuna in terms of facile synthesis of the raw material itself just as the cell membrane coating approaches. Although there is disambiguity in the sources of cells being used along with some rationale on stability issues between a synthesized particle and a natural entity, it is impeded by the gigantic therapeutic potential it is bringing in. With more and more patents and new inventions being introduced to the field, it is hard to deny that this novel biomimetic approach would go a long way to become the next generation therapeutics.

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