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Review

Applications of biomimetic nanoparticles in breast cancer as a blueprint for improved next-generation cervical cancer therapy

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ABSTRACT

Nanomedicines are innovative and promising, but lack a convincing clinical presence. Thus, biomimetic nanoparticles (BMNPs) have been designed with functionalizations which structurally and/or functionally mimic the biological setting, endowing thereupon biological structure and functionality. These may be coated with biologically derived materials, but may also include artificial antigen-presenting cells and synthetic architectures. When applied in cancer theranostics, BMNPs show significant improvements over traditional drugs and similar non-biomimetic NPs, especially in terms of circulation time, tissue penetration, delivery, and lowered toxicity. These particles have achieved unprecedented outcomes through top-down synthesis methods (cell material to NP), which bypass complex bottom-up synthetic techniques attempting to mimic such complex and diverse biological components.

Breast cancer has received much attention in this area, and as such, is studied in this paper as a template for how BMNPs could be applied in cervical cancer – an area with few BMNP applications and a dire need for efficacious and fertility-preserving therapies. This cancer remains an enormous burden globally, especially in developing countries. Being a virus-induced disease, biomimetic applications may be particularly promising, aligning with the emergence of biomimetic nanovaccines in recent years.

Feasibility challenges remain within BMNPs: Extracting biological material for re-administration to patients could cause ethical debate, and the costs involved in preparing scaled up quantities of biomimetic NPs would be large. However, with a clearer understanding and tighter characterization of preparation methods and biological responses, BMNPs may add great value to the nanomedicine community.

Introduction

Through heterogeneity and complexity in disease progression, cancers have, for centuries, remained among the most burdensome diseases with significant and persistent health, quality of life, and economical implications [1]. Perpetuating this are the numerous disadvantages and severe adverse effects of common chemotherapeutic drugs [2], as well as diverse and inconsistent treatment outcomes [3]. A major hindrance in pharmacotherapy is the inability of drugs to penetrate deep into tumor tissues and attack cancerous cells selectively [4]. In addition, many

Abbreviations: APCs, Antigen-presenting cells; AuNPs, Gold Nanoparticle; CCMFs, Cancer cell membrane fractions; CM, Cell-membrane; CT, Computed tomography; CuS, Copper sulfide; DCs, Dendritic cells; EPR, Enhanced permeability and retention; HPV, Human Papilloma Virus; LFA-1, lymphocyte function-associated antigen-1; MRI, Magnetic resonance imaging; PCL, Polycaprolactone; PDT, Photodynamic therapy; PLGA, Poly lactic-co-glycolic acid; PTT, Photothermal therapy; QD, Quantum dot; SPIONs, Superparamagnetic iron oxide NPs; TGFβR, Transforming growth factor β receptor; TNBC, Triple-negative breast cancer.

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anti-cancer drugs suffer from poor solubility, which is unfavorable for intravenous (i.v.) administration, leading to poor biodistribution and pharmacokinetic (PK) profiles, low concentration of drug at the tumor site, and conversely, higher drug concentrations in normal tissues. This leads to potentially severe adverse events [5]. The past two decades have seen a rise in engineered nanoparticles (NPs) being studied for diverse applications within oncology. NPs have been formulated with an optimal nano-ranged size, for tumor-targeting properties and reduction of the undesirable off target effects of drugs and immune therapies [6,7]. Specifically, these include the protection of drugs from biological conditions, as well as traversal of biological barriers. This lends drugs stability until the point of release in a controlled or sustained manner [8]. Liposomes, micelles, dendrimers, solid lipid NPs, metal-based NPs, and biomimetic adaptations of these, are some of the most commonly available forms. NP drug delivery systems are designed for intratumoral transport enabled by their size, charge, shape, and surface modifications. Thus, to overcome the challenge of tumor heterogeneity, NPs formulated with optimized physicochemical properties and biological materials have been used to improve blood circulation time, tumor penetration, and tumor accumulation, thereby increasing the therapeutic index of these formulations [9].

The enhanced permeability and retention (EPR) effect has been considered key to the therapeutic success of nanomedicines, whereby particles are thought to enter and be retained within tumor tissue due to fenestrations in rapidly formed vasculature and poor lymph drainage, characteristic of solid tumors [10]. However, reliance upon this phenomenon has begun to wane following repeated inconsistencies, heterogeneity between tumor types, and poor translation of this phenomenon from *in vivo* studies to the clinical situation [10,11]. It is for this reason that active NP targeting is expected to play a significant role in drug delivery and controlled release in future therapies. This may be achieved through externally conjugated peptides, antibodies, or homotypic or endogenous material, for the purpose of active targeting, improved binding, and enhancement of drug accumulation at the tumor site [12–14].

Such nanomedicines have benefitted from targeted functionalization with various polymers, achieving what is known as “stealth”, to prevent detection and subsequent clearance by the reticuloendothelial system (RES) [15]. External addition of the polyethylene glycol (PEG) molecule, also known as PEGylation, has been extensively employed as a standard protocol for prolongation of circulation. This is beneficial for passive accumulation of NPs within tumors [16]. This synthetic, biocompatible polymer prevents opsonization as well as interactions between receptors on RES effector cells and injected NPs. PEGylation has delivered breakthrough and in certain cases, market approval, for nanomedicines [17]. The PEG molecule, possessing non-ionic structure and high solubility, sterically reduces the interaction of plasma proteins with the surface of a NP [18]. However, despite the usefulness thereof, recent research in the clinic and in animal models has revealed the presence of anti-PEG antibodies (IgM and IgG) [19,20]. These can bring about severe adverse effects, including hypersensitivity reactions, potentially resulting in anaphylaxis or death. In less severe cases, these antibodies cause accelerated blood clearance (ABC) and reduce therapeutic efficacy [19,21]. A further concern related to the use of PEG is steric hindrance of interactions between NPs and cell surfaces, impacting cellular delivery [22]. One approach to overcome this is decoration of PEGylated NPs with active targeting moieties, such as an antibodies, a peptides, or receptor ligands [23,24]. However, such ligands have not shown dramatic or clinically relevant improvements in NP tumor targeting or accumulation thus far, and can actually increase ABC, thereby reducing tumor accumulation. It is at this point that improved NP functionalizations become necessary, and biomimetic functionalizations might be considered. In that way, tissue targeting is assisted by the unique properties of the cells from whence materials are extracted for external coating or functionalization [25].

Biomimetic functionalization, as a new frontier in nanomedicine, overcomes the obstacles of premature clearance, as well as poor targeting and delivery, through improved biocompatibility. This is especially needed for synthetic NPs. With such biomimetic NPs (BMNPs), true stealth elements are achieved by the endogenous and homotypic surface materials assisting RES evasion. This branch of nanomedicine benefits from important rational design elements, simultaneously endowing particles with desirable effects and bypassing significant bottom-up synthesis methodologies through addition of biologically derived (biomimetic), not only synthetic elements. Methods necessary to match the intricacy and diversity of biological material used would be prohibitively costly and complex. Such desirable structures would be arduous and largely impossible to recapitulate synthetically [26].

One area in this rapidly expanding field that has been widely studied is the BMNP-based treatment of breast cancer [27,28]. As such, this review will focus on recent studies and developments in BMNPs for effective treatment of breast cancer. When counted on the *Pubmed* database using “((biomimetic) AND (nanoparticle) AND (*cancer type*)) NOT (review)” as the search input, original biomimetic NP research articles numbered the highest on the topic of breast cancer, at 210 articles in total, published since 2009, at the time of writing, which is increasing monthly. Of the World Health Organization (WHO)’s four most common cancer types in women [29], including breast, colorectal, lung, and cervical cancers, cervical cancer had the least articles published in the above field, with only 12 articles showing some relevance to BMNPs (colorectal – 45; lung – 105). These are also two cancers following similar treatment structures in the clinic, mainly focused on surgery and radiotherapy in early stages [30]. Another angle of the rationale behind including both cancers is that both are thought to be aggravated by hormone replacement therapy (HRT) [31,32]. Whether or not these cancers arise iatrogenically is still being studied, with inconclusive results; necessitating safer, non-HRT-related approaches to treatment [33,34]. Moreover, part of the focus of biomimetic NPs is immune therapy, making Human Papilloma Virus (HPV)-caused cervical cancer a particularly interesting candidate in this field. Thus, in this review, the well-documented and explored applications of biomimetic nanotechnology for breast cancer are presented, after which these advances and observations are placed in the light of cervical cancer, with the goal of identifying potential theranostic advancements in these two primarily female cancers, through novel BMNP applications.

Current treatment modalities and potential avenues for improvement in breast and cervical cancer therapy

Prior to identifying areas of improvement achievable through nanomedicine, an understanding of current treatment modalities, and the shortcomings thereof, is necessary. Fig. 1 outlines the European Society for Medical Oncology (ESMO) guidelines for treatment of both breast and cervical cancer, at various stages [30,35]. Treatment modalities for these two cancers, could, based on a wealth of evidence, benefit from integration with nanomaterials. Surgery can make use of NPs for increased imaging potential [36], as well as nanotechnology-based detection of residual or metastasized cancerous material, also within draining lymph nodes [37]. The efficacy of chemotherapy has also been boosted through the packaging and targeting capabilities of nanomedicine [11,38–40]. NPs show significantly increased targeting, circulation time (decreased clearance), and improved volume of distribution, with reduced toxicity to normal tissues [41]. As is expounded in the sections that follow, this is especially true when biological material is utilized for similar outcomes [25]. Radiotherapy [42] and hyperthermia [22], as well as both mAb- and non-mAb-based immunotherapies [14], have also seen similar improvements once assisted by NPs. Beyond these modalities, both cervical [43] and breast [44,45] cancers stand to benefit from advances in NP-enabled gene editing and immune therapies, which are constantly being refined and improved as time progresses. Specific examples of such advances are discussed in Sections 3.1 and 3.2.

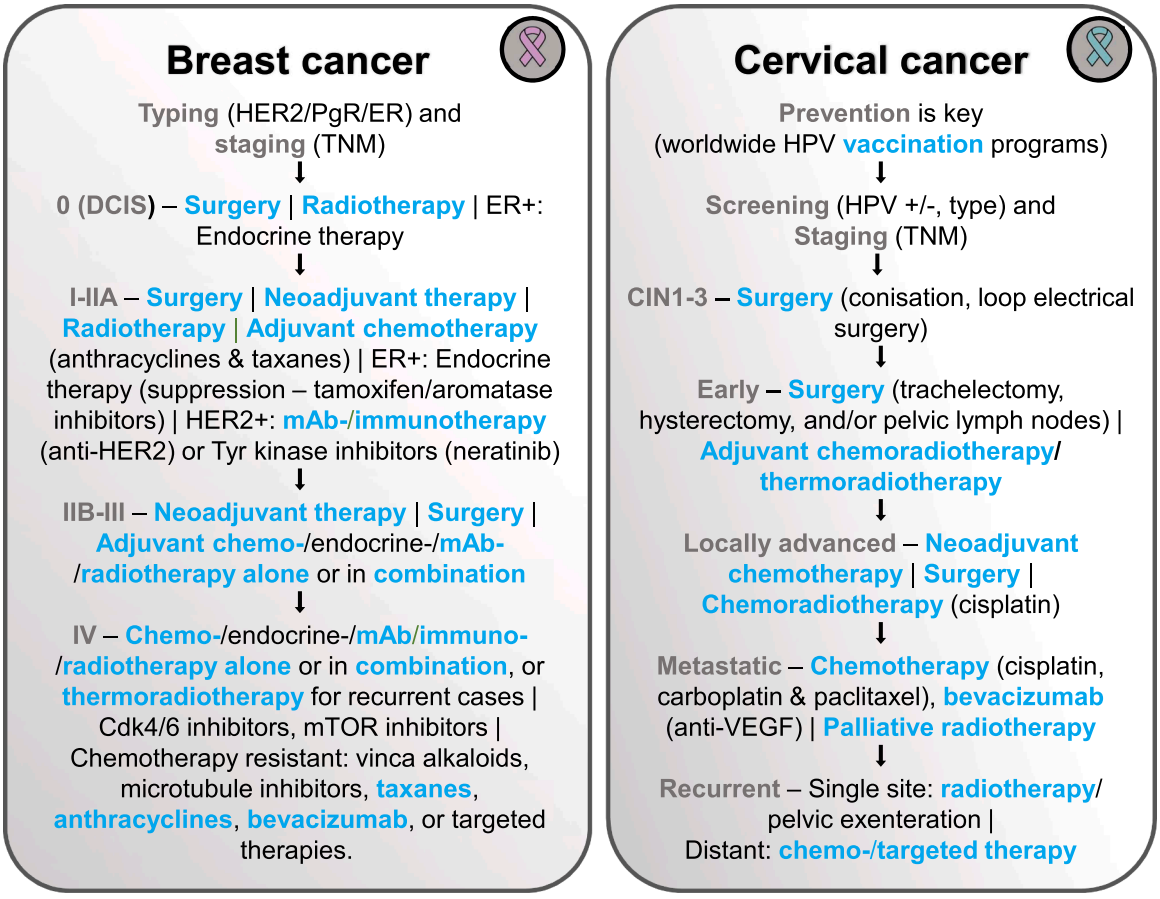

Fig. 1. Summary of clinical treatment processes and modalities for both breast and cervical cancer [30,35]. Areas in which nanomedicine (including biomimetic or other) may improve modalities are shown in blue and bold font. Abbreviations: CIN (cervical intraepithelial neoplasia); DCIS (ductal carcinoma *in situ*); ER (estrogen receptor); HER2 (human epidermal growth factor receptor 2); PgR (progesterone receptor); TNM (tumor, nodes, metastasis).
Adapted from European Society for Medical Oncology (ESMO) treatment guidelines.

NPs are also useful in investigative and diagnostic modalities. In this way, imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and photoacoustic imaging, as well as experimental theranostic techniques like photothermal therapy (PTT) and photodynamic therapy (PDT), are being utilized extensively. BMNPs have been applied to each technique in creative and synergistic ways, particularly for lowered toxicity and targeting, given that a common challenge with the above imaging modalities is unspecific targeting of imaging agents. NPs are thus being widely applied for the delivery of imaging agents [46].

Both breast and cervical cancers are classified based on various diagnostic characteristics. Types and receptors in these cancers are mentioned here for a brief background into how NPs can be designed with particular targets in mind. Briefly, cancers are assigned a stage using pathological markers, and based on defined tumor edges, presence of nodes, and metastases (tumor, nodes, and metastases method; TNM). Breast cancer patients are screened for estrogen receptors (ER), progesterone receptors (PgR), and human epidermal growth factor receptor 2 (HER2). These are key prognostic indicators and assist treatment decisions and patient stratification.

There is less receptor variation in cervical cancer; however, the causative HPV virus, in more than 80% of cases, emphasizes the importance of preventative interventions early in life, such as vaccination against HPV [47]. Worldwide vaccination initiatives and screening infrastructure availability have decreased the incidence of cervical cancer and active HPV infections in developed countries, but the same cannot be said for developing countries, where HPV and cervical cancer remain considerable burdens [35,48]. This is also linked to the nature of HPV being sexually transmitted, where education becomes important in preventing the spread thereof. Furthermore, in the last five years, many more people have begun resisting or becoming skeptical about vaccination. This may be due to notions propagated by the media, or cultural and religious stances, further empha curative or suppressive actions against cervical cancer remain necessary.

Biomimetic Nanoparticles

The structures of BMNPs may be designed with organic or inorganic material cores to increase bio-interfacing capabilities for desired purposes [49]. Organic materials include polymers such as poly (lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), as well as various lipid molecules (liposomes, lipid nanoparticles). These biodegradable cores are used for delivery of both hydrophobic and hydrophilic theranostic payloads [50]. Inorganic materials such as copper sulfide (CuS), gold NPs (AuNPs), MOFs, and iron oxide (Fe_3O_4) NPs can be synthesized with porosity, allowing improved drug loading capability. Moreover, these NPs possess unique magnetic, electrical, and optical properties, which are commonly applied in biomedical procedures for imaging or as diagnostic tools [51].

BMNPs feature an array of biologically-derived functionalizations, mostly with materials of tissue, cell membrane, or organelle origin [52,53]. This can include peptides, antibodies, and cell membrane components, resulting in increased bioavailability, prolonged circulation, and selectively increased interactions with the tumor microenvironment (TME) or selected organs [54–56], through mimicry and tissue tropism [57]. Specific cell membranes are chosen for unique advantages and

potential membrane receptors present on these cells [58]. Briefly, tumor cell membranes add homotypic targeting and adhesion *via* tissue tropism and cadherin presentation, and may introduce tumor antigens onto the surface of BMNPs. Immune cells add endothelial adhesion and thus, potential targeting of tumors due to the EPR effect, as well as immunogenic signaling markers such as lymphocyte function-associated antigen-1 (LFA-1), as well as functional proteins such as the membrane attack complex (MAC-1). Red blood cells add immune evasion and long circulation capabilities, and may carry CD47's "don't eat me" signal onto the BMNPs [58]. Mesenchymal stem cell (MSC) membranes can increase tumor cell targeting and interactions, as well as stability, biocompatibility, immune escape, and longer circulation [4]. Lastly, Platelet membranes, from the blood components that prevent excessive blood loss following blood vessel injuries, enable escape from RES uptake and increase adherence to pathogens and endothelial tissues. This is due to platelets' normal key role in cancer invasion and metastases. This is through generation of platelet-cloaked circulating tumor cell (CTC)-aggregates and stimulation of CTCs to adhere to endotheliocytes, shielding the CTCs from immune cells [59]. P-selectin is overexpressed on the surface of platelets, allowing BMNPs to bind to CD44 receptors on the surfaces of stem cells and cancer cells [60] (Fig. 2).

There have been numerous studies focusing on other types of BMNPs as well, such as those functionalized with peptides, for cancer treatment [61,62]. For example, the peptide iRGD, by binding to the αvβ3 and αvβ5 integrins, can enhance targeted cancer therapy that can significantly increase the efficacy and safety of the therapeutics. This was demonstrated in a study by Bressler et al. with aPLGA-PEG NPs decorated with AXT051 collagen-IV derived peptides with both antitumor and antiangiogenic properties. The *in vitro* study of constructed NPs demonstrated significant inhibition of proliferation of human triple-negative breast cancer cells and microvascular endothelial cells *via* binding to integrin αvβ3 receptor [63]. Another example involving coating NPs with CD63-aptamers (single strand oligonucleotides targeting lysosomes) which can used for treatment of cancer. In a such study, metal-organic frameworks (MOFs; ZIF-8) were fabricated with Zn^{2+} ions which connected by 2-methylimidazole bridging units, were coated with a lysosome-targeting aptamer and incubated with T cells. *In vivo* assessment using 4T1 tumor-bearing mice demonstrated that significantly prolonged mice survival [64].

Advantages and disadvantages of biomimetic nanotherapies

BMNPs are designed to mimic the composition and functionality of natural structures, with the following advantages:

First, the enhanced stability of biomimetic nanoparticles, afforded by inclusion of biological structures onto these particles, makes them more resistant to degradation and able to maintain their structure and function over time within biological systems. Second, BMNPs' improved targeting ability allows selective binding to target cells or tissues, as they can be engineered with particular ligands or receptors from donor tissues. This targeting ability reduces off-target effects while increasing agents' presence in desired areas [65,66]. Third, BMNPs are more compatible with living systems because they closely resemble biological structures. This allows better tissue penetration into deeper tissue layers. Fourth; structurally, BMNPs may lower the possibility of an immune reaction or toxicity compared to regular NPs. This makes them safer and less immunogenic for use in medical and biological applications [67]. Fifth, biomimetic strategies enable precise management of and communication with biological systems through rational design. To achieve desired results, such as controlled drug release, effective cellular

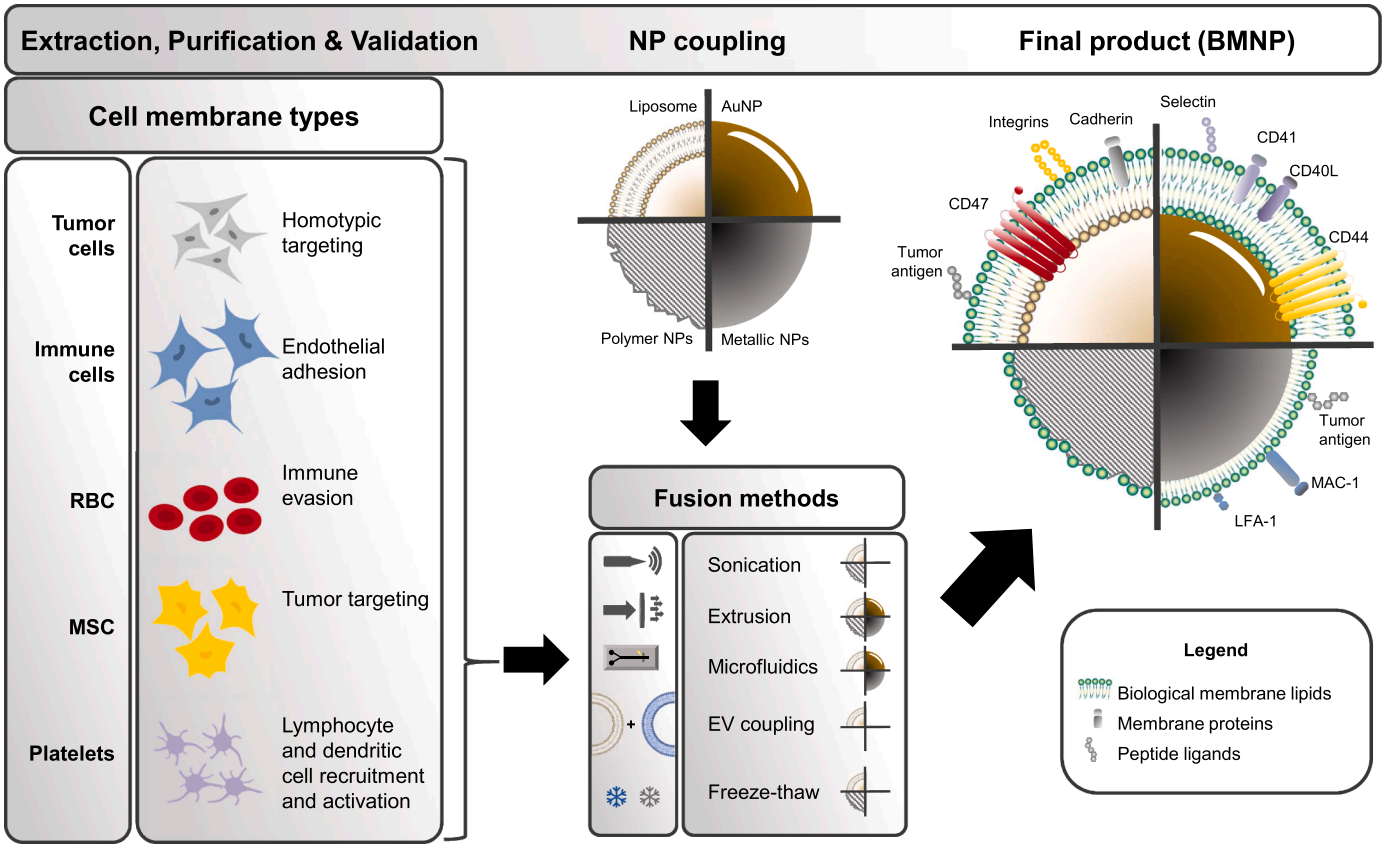

Fig. 2. An overview of the different cells used for membrane material extraction, which is then transferred to NP of various kinds. Fusion methods are summarized, including which methods are used for which type of NP core. Lastly, a schematic visualization is provided to show the transfer of membrane receptors onto BMNPs. Abbreviations: RBC, red blood cell (erythrocyte); MSC, mesenchymal stem cell; NP, nanoparticle; EV, extracellular vesicle (exosome); CD, cluster of differentiation; MAC, membrane attack complex; LFA, lymphocyte function-associated antigen.

uptake, or tumor accumulation, researchers can customize the composition, size, and surface properties of nanoparticles [68]. Sixth, BMNPs may potentially be used in personalized or individualized medicine approaches whereby patients' tumor biopsies are used to extract coatings or patient specific tumor antigens to increase autologous therapeutic vaccination and deeper tissue penetration.

However, despite significant progress in the development of various membrane-mimicking strategies, there are still several challenges slowing BMNPs' progression to clinical trials. A great deal of work is anticipated to develop these BMNP while avoiding their undesirable drawbacks, such as difficult synthetic and purification processes, a lack of standardized protocols for preparation and isolation in sufficient quantities, and potential safety and immunogenicity issues in the human body. This includes the following set of drawbacks:

First, the production of BMNPs is often challenging to scale up to larger quantities. These particles' potential applications may be constrained by the complex fabrication processes used. Second, BMNPs may have limited storage stability, especially when exposed to harsh environmental conditions. Over time, they may degrade due to contact with virus and pyrogen contaminants, as well as potential damaging temperature, pH, or humidity conditions. These parameters would also need to be optimized for new formulations. Third, BMNPs are intended to be biocompatible, but there is still a possibility of toxicity or unfavorable reactions when they are introduced to living systems. It is essential to carefully consider potential side effects resulting from the intricate interactions between BMNP and biological systems. Fourth, the safety and efficiency of these particles need to be thoroughly assessed before they can be approved for use in humans, which can significantly delay their translation from the lab to real-world applications. Rationally designed, novel particles such as these, may need more in-depth studies in this area. Fifth and lastly, high cost factors can limit BMNPs' marketability and hinder their widespread adoption. Production and purification of BMNP can be expensive due to specialized equipment, materials, and expertise required.

In the following section, preparation methods and physicochemical properties are briefly summarized before entering into the biological applications of BMNPs.

Preparation methods

There are a range of methods available for fusing the biomimetic material and NPs, with diverse applications [69]. Here, the commonly reported fusion methods are discussed, which, in the preparation pipeline, would take place after extraction and purification of desired biological material, which, for cell membranes, is typically achieved through dialysis and solubilization [70]. The main criterion is electrostatic or covalent interactions between the NP core and the biological coating, to generate a stable core-shell structure [71]. Key aspects of the successful preparation of biomimetics, enabling accurate biomimicry in composition and topological conformation, and thus, function, are retention and correct orientation of membrane receptors on the NP exterior – a cumbersome but important characteristic to measure, typically done using transmission electron microscopy (TEM) or more indirect methods including functional assays [70,71].

Sonication

Sonication (Fig. 3a) involves biological macromolecules being fused with the organic or inorganic NP cores, through exposure to frequencies of ultrasonic energy between 20 kHz and 1 MHz, though the optimal frequency should be sought for fusion of specific formulations and downstream applications. Many examples of sonication exist in literature but it remains a less precise method of BMNP preparation due to random energy distribution, causing variations in yield. This can also be due to heat being introduced to the system by the ultrasonic energy waves, possibly causing denaturation and damage to biological elements [70,72].

Co-Extrusion

Co-extrusion is one of the most frequently employed methods for biomimetic NP preparation. In this technique, a suspension of biological material and NP cores is passed under pressure through micro- and nanosized pores [75]. This causes disturbance of the membrane's structural integrity, resulting in breaking and reformation around the NP core. Extrusion results in a more homogeneous and favorable size, depending on parameters such as membrane pore size, number of cycles, and pressure applied. Extrusion is suitable for small-scale production.

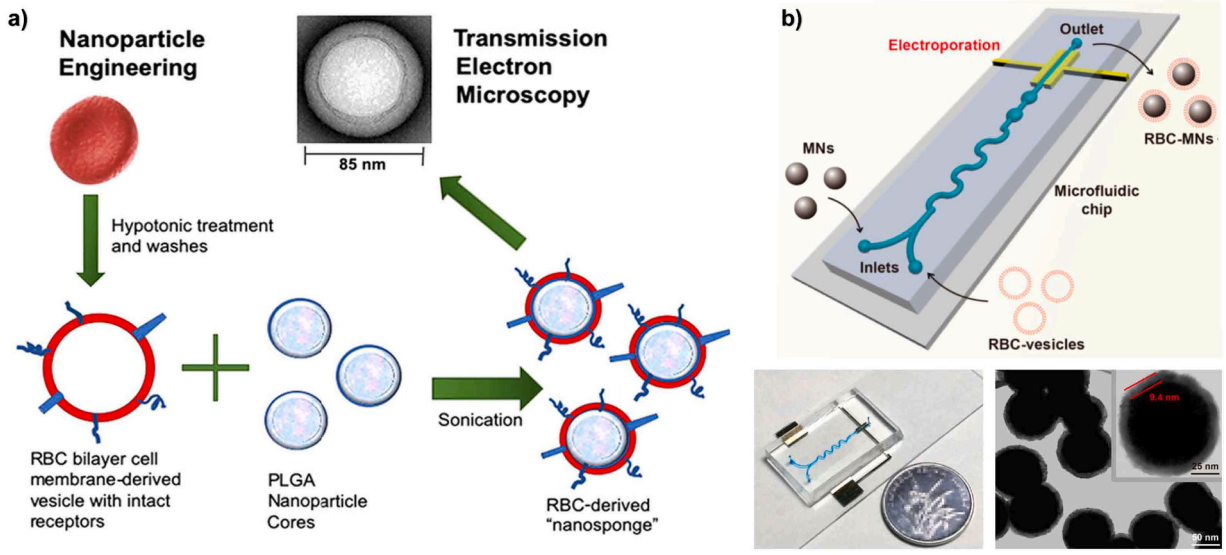

Fig. 3. a) Schematics demonstrating fusion of an erythrocyte-derived ghost membrane vesicle and PGLA core to create nanosponge therapeutics using sonication. A representative TEM image of the resulting nanosponge is also shown. b) Preparation and administration schematic using microfluidics to fuse magnetic nanoparticles (MNs) with the erythrocyte membrane. Actual size of device, as well as micrograph of product also shown. Abbreviations: PLGA (poly(lactic-co-glycolic acid) nanoparticles); RBC-MNs (red blood cell membrane-functionalized magnetic nanoparticles).
(a) Adapted from Koo et al. [73], licensed under CC BY 4.0 http://creativecommons.org/licenses/by-nc/4.0/. (b) Reprinted (adapted) with permission from Rao et al. ACS Nano 2017, 11, 4, 3496–3505. Copyright (2017) American Chemical Society [74].

Using this method for large-scale production poses a challenge, being inefficient in comparison to sonication [76]. Erythrocytes were the first type of cell membrane to be isolated by hypotonic treatment and conjugated to negatively charged polymeric NPs through co-extrusion [50]. An extrusion schematic is shown in Fig. 5a later in the manuscript [77]. An example of sonication combined with extrusion was demonstrated by Hu et al., is erythrocyte membranes being collected from whole blood in a hypotonic buffer, at a frequency of 42 kHz for 5 min [70]. These were then coated over PLGA NPs using extrusion. In this way, disruptive forces from the applied pressure facilitated the breaking of PLGA NPs through the lipid bilayer, which led to fusion of the NPs and biomimetic layers, spontaneously forming BMNPs [72].

Microfluidics

The science of microfluidics is known as high throughput technology capable of integrating the biological materials onto NP cores *via* the site of entry being coated in cell membrane-derived vesicles (Fig. 3b) [78]. This method is highly efficient and may be applied for microliter volumes, or extensively scaled up. An example of this approach, which involves quick mixing of NP and biomimetic vesicles followed by electroporation, whereby an electric field is applied to the NPs to momentarily increase permeability and control movement of charged particles, has been employed to coat biomimetic cell membrane layers onto magnetic NPs [74]. Microfluidic methods enable higher quality production and stability, therefore possessing marked advantages, including relatively high throughput, quantitative control, homogeneity of output, and predictability [74]. However, this procedure is substantially more expensive than the previous two processes; thus, also introducing feasibility challenges [79].

Other novel preparation methods

Combinations of the above are commonly used for BMNPs preparation. Such combinations can include sonication with extrusion, extrusion with electroporation, and others [80]. Freeze-thaw is also a common method, but usually requires coupling with more precise methods to reduce heterogeneity of resultant particles [14,80,81]. On the semi-synthetic side, methods such as *in situ* packaging involve exposing cells with nanomaterials of various kinds and inducing cells to secrete hybrid semi-synthetic BMNPs [72,82]. This methodology resembles the extraction, or harvesting, of extracellular vesicles (EVs), also known as exosomes, secreted by cells naturally under certain conditions [83]. These subcellular constructs have seen extensive use in recent oncology research and readers are here referred to excellent reviews on the topic by Busatto et al. on the secretome of cells [83], Zhang et al. on therapeutic uses thereof [84], and Hamzah et al. on theranostic applications of exosomes [85].

Physicochemical properties and characterization

The physicochemical properties of all types of NPs, BMNPs being no exception, affect the way in which such particles interact with biological systems [86]. NP immune cell attraction (leading to ABC) is the most affected by these. Ilinskaya et al. investigated this phenomenon with respect to the immunogenicity of the PEG molecule on the exterior of NPs, reporting that larger micelles (>50 nm) as well as liposomes bearing the PEG molecule induce ABC, but not smaller micelles [87,88]. It was also mentioned that NP charge did not affect ABC [89]. However, charge shows a more indirect effect, as non-neutral NPs tend to adsorb more serum proteins, forming a protein corona around the particles, which in turn increases the hydrodynamic diameter thereof [90]. Thus, the increased size as a result may cause increased ABC. PEG density has also been listed as a possible factor affecting ABC, with contradictory findings; for example, 5% PEG induced higher ABC than 10–15% PEGylated NPs in one study [91], but another study noted stronger ABC against 9% PEGylated liposomes than 3% [92]. Aside from PEG, NPs may also attract opsonins and Fc or antigen receptors on diverse immune cells, triggering phagocytosis or cytotoxic responses, followed by clearance or destruction [93]. This effect could potentially be amplified by externally conjugated targeting moieties including antibodies, peptides, or antigens, which could further attract immune cells [14,24].

While conventional NP circulation time and biodistribution are influenced by shape, size, and surface charge, BMNPs utilize other characteristics in addition to these, such as homotypic or infiltrative targeting, and increased tissue compatibility [13,94]. It is important to validate the optimum size and surface charge (zeta-potential) of NPs after adding biomimetic elements. Increases in size, and alterations to surface charge, are observed with such coatings. Particle size is commonly measured using dynamic light scattering (DLS) or NP tracking analysis (NTA) and may be validated using TEM, whereby the particles coated with cellular lipid bilayers are clearly visible and measurable [95,96]. Identification of the principal protein components of the membrane coatings of NPs is typically done by SDS-PAGE and western blots [70,97]. Lastly, the sizes of NPs (expounded in Table 1) facilitate passage through pores of endothelial structures, or retention within tissues [27,28,98]. The complex interplay between all of the above elements facilitates increased therapeutic efficacy, and the mechanisms by which that is achieved are diverse and innovative. Biological responses to such treatments are explored further in the next section.

Oncological applications of biomimetic nanoparticles

Biomimetic breast cancer nanotherapy

Breast cancer, the most frequently occurring carcinoma, and a prominent cause of mortality among females [29], is regarded to be treatable in early stages, prior to presence of distant metastases, after which treatment becomes substantially more complicated [107,108]. Metastasis is promoted by acidity and hypoxia in the TME, as well as upregulation of hormone receptors which assist or induce angiogenesis and growth, and suppress the immune response [109]. In addition, the human epidermal growth factor receptors are of interest, also known as c-erbB or HER-1, as well as HER-2, HER-3, and HER-4 [110]. HER-2 is overexpressed in 20–30% of breast cancer cases, the expression of which is associated with poorer prognoses [111]. The TME, comprising proliferating tumor cells, extracellular environment matrix (ECM), immune cells, and cancer-associated fibroblasts (CAFs), can also modulate the response of a tumor to treatment [112]. CAFs are a major part of the TME and release large amounts of cytokines and growth factors which increase angiogenesis, tumor cell proliferation, and induction of ECM remodeling. Recent developments in nanotechnology have included alteration of NPs with CAF-derived ligands, enhancing penetration and accumulation of nanodrugs within tumors, through the reduction of interstitial fluid pressure and inhibition of angiogenesis, drug resistance, and immunosuppression in the TME [112].

In vitro and in vivo experimental biomimetic breast cancer nanotherapies

Nanomedicine has brought about improvements in diagnosis and treatment utilizing features of the TME for breast cancer therapy. A good example of this is activated fibroblast (AF) membrane-coated biomimetic semiconducting polymer NPs (AF-SPNs) which were not only homologously targeted towards CAFs, but comprise highly NIR-absorbent material, giving these NPs phototheranostic capabilities [113]. However, major challenges like metastasis and resistance to therapy remain, which prevent efficacious treatment. Rational design of natural and synthetic BMNPs, as well as progress in the study of cellular behavior of cancers permits useful targeting and bio-interfacing in complicated biological frameworks [114].

The ability of BMNPs to enable coordination of various components to address various therapeutic targets has inspired top-down biomimetic approaches utilizing cell-membrane-derived vesicles (CMs) as a functional unit. Sun et al. developed NPs composed of PCL and Pluronic®

Table 1
Classifications and physicochemical characteristics of common representative biomimetic nanoparticles and the differences in size and charge between the nanoparticle core and the added biomimetic elements. Abbreviations: HER2 (human epidermal growth factor receptor 2); iRGD (cyclic 9-amino acid peptide based on arginylglycylaspartic acid); NPs (nanoparticles); NSCLC (non-small-cell lung cancer); PLGA (poly(lactic-co-glycolic acid); siRNA (small interfering ribonucleic acid); TME (tumor microenvironment).

Biomimetic material		Nanoparticle composition	Size (nm)		Zeta potential (mV)		Outcome	References
			Nanoparticle	Biomimetic nanoparticle	Nanoparticle	Biomimetic nanoparticle		
Erythrocyte		Paclitaxel loaded in polycaprolactone NPs	133	147.9	- 6	-16.1	NPs coated with membrane in combination with iRGD enhanced perfusion into breast tumors	[99]
		Paclitaxel loaded in poly (γ-glutamyl cysteine) NPs	50	100–130	–	–	pH sensitivity of biomimetic NPs demonstrates effective strategies for acidic breast cancer TME-targeted drug delivery	[100]
Cancer Cell	**HeLa**	Doxorubicin in combination with Ca^{2+}-channel-inhibiting SiRNA chitosan NPs	100	122.39	+ 25.32	-27.76	Enhanced targeted NSCLC tumor delivery in comparison to delivery without biomimetic	[101]
	MCF-7	Curcumin in combination with chlorin e6 were loaded into PLGA NPs	193	202	-34	- 25	Synergistic breast tumor therapy through combination chemo-/phototherapy	[102]
	CHO	Mesoporous silica loaded with Doxorubicin modified by glycosyl-phosphatidylinositol-anchored anti-HER2 scFv antibody fragments	100	–	-19.3	+ 0.1	Significant inhibition of breast tumor growth	[103]
Platelet		Paclitaxel in chitosan	115	128	–	–	Targeting signal amplified and accumulation in tumor site enhanced anti-breast-tumor efficacy	[104]
		PLGA NPs	–	+ 15	–	–	Decreased uptake by immune cells and selective adhesion to damaged human cells (breast cancer model)	[105]
Neutrophil		Doxorubicin in combination with SM (Shanzhiside methyl ester) loaded in mesoporous silica NPs	50	120	-32.6	-21.7	High drug-loading capacity and anti-lymphoma tumor efficacy, and anti-inflammatory properties	[106]

copolymer F68, loaded with paclitaxel and functionalized with CMs extracted from the 4T1 murine breast cancer cell line. These particles showed accumulation in primary and metastatic cancers and significantly inhibited tumor growth and metastases, compared to non-biomimetic variants of the same NPs [94]. In another study, PLGA NPs coated with human cancer cell membrane fractions (CCMFs), prepared by extrusion through porous membranes, showed that the internalization thereof disrupted the migration of human mammary fibroblasts and decreased metastatic burden [115]. This has also been applied in triple-negative breast cancer (TNBC), a highly invasive cancer type, associated with aggressive growth and short survival time lacking the above cellular receptors [116] Due to this lack of targetable receptors, chemotherapy has remained the primary treatment modality [117,118]. In another study, BMNPs were designed with the antitumor and anti-angiogenic peptide AXT050, and activity was determined *via* proliferation of human TNBC (MDA-MB-231) tumors *in vivo*. Results indicated strong interactions between the surfaces of cancer cells and AXT050-coated PLGA NP, showing potential for application in cancer therapy [63]. TNBC has also received attention from biomimetic gene therapy. A novel drug delivery-based DNA therapeutic was evaluated by Ma et al., using an anti-HER-2 aptamer. This was synthesized by modifying tetrahedral framework nucleic acids (tFNA) (denoted as HApt-tFNA) for delivery of the chemotherapy agent maytansine (DM1). Conjugation of DM1 produced the novel carrier HApttFNA@DM1 (HTD), able to target the HER-2 protein and deliver drugs preferentially into tumor cells. In order to increase the halflife of DNA-based drug delivery agents, an erythrocyte CM-coated liposome, including pH sensitive fusogenic lipids (PEOz), was incorporated into the hybrid erythrosome nanocarrier. The circulation time of PEOz-erythrosome in comparation of PEO-z-liposome was significantly increased, leading to tumor-stimulated drug release and improved safety over non BMNP formulations. The study of anti-tumor efficacy showed considerably better results due to the longer circulation and higher biocompatibility than other groups [119].

For example, platelet membrane-coated PLGA NPs were used in combination with PTT and chemotherapy: doxorubicin (DOX) and indocyanine green (ICG; as a PTT agent) were co-encapsulated into BMNPs for targeting of MDA-MB-231 tumors *in vivo* [120]. Results showed high affinity of P-selectin platelet-covered NPs to CD44 ligands on tumor cells, and a lack of lung micrometastases after treatment, evidenced by H&E staining of lung slices. These BMNPs acted as suitable targeting ligands for deep lymph node penetration with effective metastasis inhibition [120]. The aforementioned expression of P-selectin on platelets can also interact with P-selectin glycoprotein-1 on leukocyte membranes, mediating leukocyte rolling on the endothelium [121]. Zhang et al. designed a novel platform exploiting this, consisting of hybrid leukocyte/platelet-membrane-coated dendritic large pore mesoporous silica nanospheres (DLMSN) (Fig. 4a-b). These DLMSNs, though a different nanoplatform, also aimed to co-administer DOX and a PTT agent (NIR-fluorescent dye, IR780), for synergistic therapy. Hybrid leukocyte/platelet membranes are able to interfere with LFA-1/ICAM-1 interaction-dependent tumor vasculature and tissue penetration, as well as p-selectin/CD44 binding-mediated tumor cell targeting [122]. In this study, combination treatment of PTT/PDT and DOX in 4T1 cells demonstrated synergistic cytotoxicity and apoptosis induction, as well as significant tumor suppression. A reduction of recurrence in TNBC

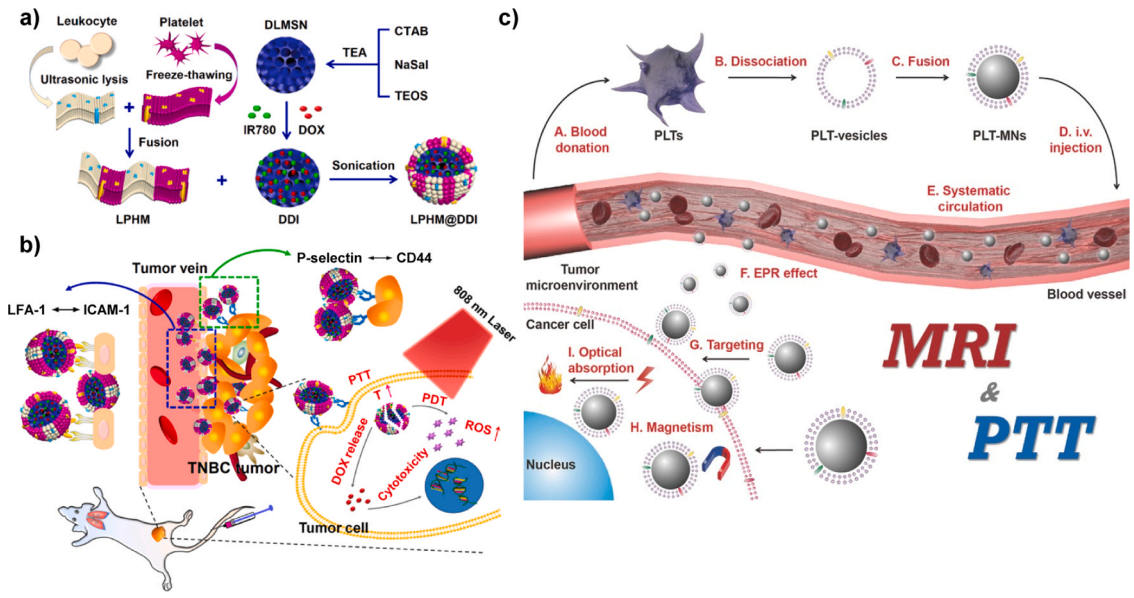

Fig. 4. **a)** Schematic of methods of preparation of LPHM@DDI NPs and **b)** the PTT/PDT-chemotherapy synergism thereof observed in triple-negative breast cancer. **c)** A similar schematic shows uses of mouse platelet-membrane functionalized magnetic iron oxide nanoparticles for both PTT and MRI applications in vivo. © 2017 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. **Abbreviations**: DLMSN (dendritic large pore mesoporous silica nanospheres); TEA (triethyl amine); CTAB (cetyl trimethyl ammonium bromide); NaSal (Sodium salicylate); TEOS (tetraethyl orthosilicate); PTT (photothermal therapy); PDT (photodynamic therapy); PLT-MNs (platelet-membrane-functionalized magnetic nanoparticles); LPHM@DDI NPs (leukocyte/platelet hybrid membrane and dendritic large-pore mesoporous silica nanoparticles with near infrared fluorescent dye and doxorubicin).
(a) Adapted from Zhang et al. [122], licensed under CC BY 4.0 http://creativecommons.org/licenses/by-nc/4.0/. (b) Reproduced with permission from Rao et al. [123].

mice *via* tumor ablation and anti-angiogenesis was also observed upon rechallenge with tumor cells.

Lastly, macrophages exert significant influence on tissue development and homeostasis: conditions which influence the development and metastasis of cancers [124]. Thus, biomimetic coatings of hybrid RAW264.7 and 4T1 CMs, as well as macrophage membranes, were combined with DOX-PLGA NP cores *via* sonication by Gong et al. [125]. Their approach successfully endowed NPs with desirable anti-metastatic activity in breast cancer, achieved through accumulation at sites of inflammation and specific targeting of 4T1 lung metastases due to tissue homogeneity.

Biomimetic theranostic and multimodal therapies for breast cancer

Recent research has shown that the use of BMNPs as carriers provides an effective delivery platform for both therapeutic and diagnostic applications. Rao et al. synthesized and studied mouse platelet-membrane functionalized magnetic iron oxide NPs for both PTT and MRI applications *in vivo* (Fig. 4c) [123]. These NPs showed increased circulation time and cancer targeting capabilities, and since they are donor-derived in nature, were immune-compatible with the mice in the study. Interestingly, it was found that PTT treatment also further guided the NPs toward treated tumor sites. This was serendipitously discovered, and the researchers concluded that the blood vessel damage induced by PTT attracted the platelet membrane-coated particles, in line with the normal function of platelets to repair vascular damage. This further increased the efficacy of these BMNPs, and serves as an excellent example of a biomimetic element retaining a key biological function and thereby adding to the therapeutic potential [123].

In a study by Liang et al., an erythrocyte membrane-coated black phosphorous quantum dot (QD) formulation was tested for immuno-PTT of breast cancer. BMNPs induced apoptosis of 4T1 tumors upon NIR laser radiation. Further study showed that these NPs used in combination with immune checkpoint-inhibitors reduced residual tumor tissue and inhibited both primary and secondary breast tumor growth [126]. Incorporation of homotypic targeting elements using cancer CM coatings utilized for diagnosis and PTT demonstrated immune escape and homotypic targeting ability. In one such case, paclitaxel and superparamagnetic iron oxide NPs (SPIONs) were loaded into biomimetic cancer cell mesoporous silica NPs (MSNs) for therapy of breast cancer (MDA-MB-231) tumors. This combination of magnetocaloric and chemotherapy showed the potential of biomimetic MSNs for such treatments in breast cancer [127]. Further to this, a hybrid coating of erythrocyte and mouse melanoma CMs (RBC-B16F10) was applied to copper sulfide (CuS) NPs for treatment of melanoma in combination with chemo-PTT. Results showed a prolonged circulation lifetime with increased ability to recognize homotypic cells, owing to the long circulating properties of erythrocytes and homogeneity of tumor membranes, respectively [128]. Lastly, a study by Liang et al. investigated macrophage-membrane-functionalized biomimetic liposomes loaded with quaternary alloy (Zn-Ag-In-Se/ZnS) QDs as imaging agents. These QDs were loaded into the phospholipid bilayer and the hydrophilic chemotherapeutic DOX was loaded into the aqueous interior. These liposomes enabled immune evasion and showed potential for both image-guided surgical interventions and chemotherapy [129].

Such studies are of particular interest in the current landscape of nanotechnology working together with imaging modalities in the form of image-guided drug delivery, to increase efficacy of drugs while lowering the toxicity thereof in a smart and precise manner [130]. This is of particular importance due to the extreme toxicity induced by such therapies with current modalities. In subsequent sections, biological interactions and immune applications are discussed.

Pharmacokinetic studies in breast cancer

NPs are designed primarily to improve the pharmacokinetics of drugs introduced to the body; thus, the stability of BMNPs is crucial for effective drug delivery. Generally speaking, NPs have shown promising targeting to, and accumulation in, tumor tissue due to the EPR effect: however, more active delivery methods are preferably being sought, as the EPR effect is poorly conserved between different individuals and different tumor types, and is thus unreliable [131]. *In vivo*

biodistribution is most conveniently quantified using fluorometry, UV–vis absorption, and inductively coupled plasm-mass spectrometry (ICP-MS), as well as imaging technology such as confocal microscopy and matrix-assisted laser desorption ionization-imaging mass spectrometry (MALDI-IMS) [132]. For example, in a study by Chen et al., ICG-loaded NPs with cancer CM-coatings (ICNPs) showed reduced interception and clearance by the kidneys and liver, due to the endogeneity of the biomimetic surface. For dual-modality imaging by near infrared fluorescence and photoacoustic imaging, high resolution and deep penetration *in vivo* was observed for real time imaging (Fig. 5a–c) [77]. As another example, animals given DOX and IR789 (as an imaging agent) incorporated into PLGA NPs showed more than double the circulation time when the same NPs were coated with platelet membranes, demonstrating the power of the biomimetic aspects of these novel imaging agents (platelet membrane-NPs: 30.80 h, bare NPs: 12.97 h) [133]. Further examples of BMNPs for breast cancer treatment which have progressed to the clinic are shown later in the paper, in Table 3.

Biomimetic nanovaccines and immune therapies in breast cancer

NP-based vaccine delivery has gained much attention in recent years, owing to the unique characteristics thereof including size, charge, surface-to-volume ratio, and importantly, the ability to successfully deliver nucleic acids or protein components in a protective manner. To this end, many nanovaccine formulations with a variety of targets and designs have been developed [134,135]. Nevertheless, nanovaccines have been less frequently applied for cancer therapy than for other

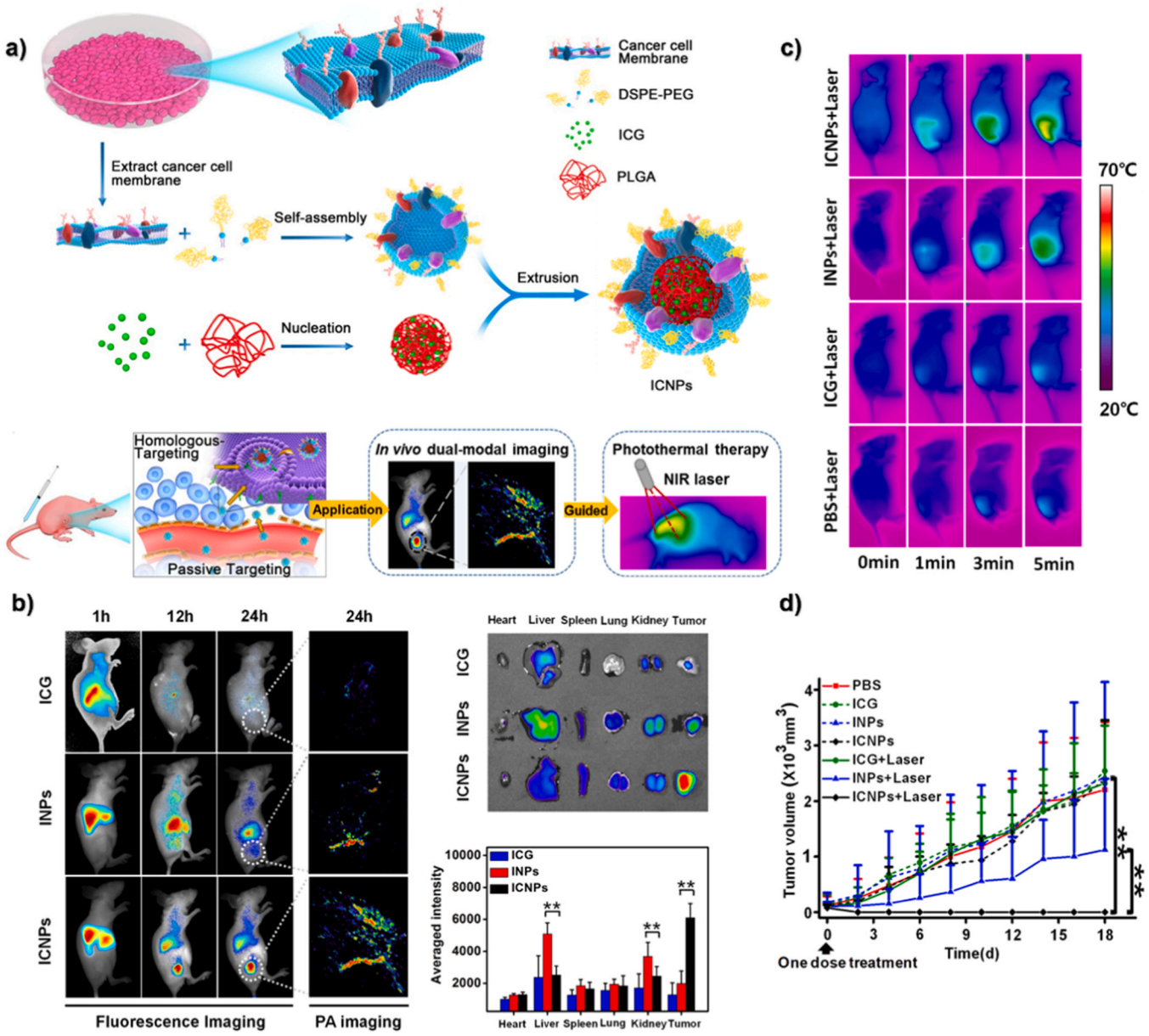

Fig. 5. a) Study schematic of homologous cancer-targeting ICNPs for dual-modal imaging-guided PTT. b) In vivo biodistribution of homologous-targeting ICNPs after intravenous injection, including time lapse near-infrared fluorescence and photoacoustic images of nude mice. c) IR thermal images of MCF-7 tumor-bearing mice exposed to an 808 nm laser for up to 5 min show efficient tumor-targeted PTT. d) MCF-7 tumor growth curves of different groups after treatments. Through specific homologous targeting and the EPR effect, ICNPs realized high levels of tumor accumulation, dual-modal imaging, and effective PTT and tumor control after intravenous injection. Abbreviations: ICG (indocyanine green); DSPE-PEG (1,2-diastearoyl-sn-glycero-phospho-ethanolamine-polyethylene glycol); PA, photoacoustic; PLGA (poly(lactic-co-glycolic acid)); ICNPs (ICG-loaded, cell membrane-functionalized nanoparticles); PBS (phosphate-buffered saline).
(d) Reprinted (adapted) with permission from Chen et al. ACS Nano 2016, 10, 11, 10049–10057. Copyright (2016) American Chemical Society [77].

diseases. Such cancer vaccines are outlined in a recent review by Addeo et al. [136]. Cancer vaccine delivery agents have been designed to target tumor cells, dendritic cells (DCs), or to deliver antigens or a variety of immunoadjuvants. Due to challenges including low stability and induction of potent immunosuppressive responses, the desired therapeutic response from such nanovaccines has been hindered [137]. In this regard, biomimetic functionalization has been applied to nanovaccines, which now represent a novel class of NPs [138,139]. Favorable features of biomimetic nanovaccines include co-delivery of adjuvants and antigens, as well as unique physicochemical properties. These include size and ability to extend circulation through evasion of the immune response, through functionalization with various biological and biomimetic elements [140,141]. This is an ideal answer to subunit vaccines being limited in use due to insufficient targeting. In these applications, it is common for a very large fraction of injected vaccine material to be sequestered and removed from circulation without entering the lymph nodes, where T cell training and clonal expansion can bring about an efficacious immune response [142]. Targeting to certain tissues, be these lymph nodes or tumors (for *in situ* vaccination applications) can assist in lowering dose of vaccines, which can reduce adverse events, potentially eliminate the need for adjuvants, and greatly reduce costs involved with global vaccination efforts.

Biomimetic nanovaccine formulations can comprise a range of molecules including proteins, lipids, polymers, and nucleic acids, around or within a nanoparticulate core. Additionally, antigens and adjuvants can be loaded into NPs in combination or separately to retain the integrity of these molecules. Coating NPs with cancer cell membranes, while assisting delivery and targeting, can inherently include nanovaccine activity due to presence of a range of membrane proteins which include antigens, potential neoantigens, and adjuvant molecules [142]. NPs can also assist in cross-presentation to antigen-presenting cells (APCs), causing drainage into the lymphatic system where the density of immune cells is desirably high [142,143]. There is also potential in this area for personalized medicine approaches whereby patients' tumor biopsies are used to extract coatings to increase autologous therapeutic vaccination effects.

Three examples of the above exist in studies by Kroll et al. [97], Yang et al. [144], and Fang et al. [145]. These studies all assessed similar B16-F10 mouse melanoma membrane-coated PLGA nanovaccines in immune-competent mice. The nanovaccines were loaded with the adjuvants CpG, to increase the immune response, a toll-like receptor (TLR) 7 agonist and a mannose surface-modification for APC recognition, or monophosphoryl lipid A (MPLA), respectively. The three groups observed promising prophylactic and therapeutic effects, including strong localized induction of pro-inflammatory cytokines IL-6 and IL-12, DC maturation, as well as T cell activation confirmed by tetramer formation [97]. These effects indicated a successful outcome, but survival was not desirably increased, due in part to vaccination having to overcome a strongly immunosuppressive environment. Thus, a combination of CTLA-4 and PD-1 blockade was added to therapy to boost the therapeutic effect in a synergistic manner. The combination brought about significantly increased survival of over 50% of animals beyond 50 days. This was compared to checkpoint inhibition (non-significant increase, but still a notable effect) and BMNP vaccines (significant effect) alone. However, a separate study showed a significant improvement over singular PD-1 inhibition, and over BMNP vaccines without PD-1 inhibition [144]. Jin et al.also coated similar NPs with human glioblastoma (U87MG) and breast cancer (MDA-MB-231, BT-474) cell membranes. They observed draining lymph node-localization and increased CD8 + and CD4 + T-cell counts in immunocompetent mice.

Other lipid-based biomimetic nanovaccines were synthesized by Wen et al., structurally resembling high-density lipoprotein (HDL) [146]. These were prepared using phospholipids and apolipoprotein A-1 extracted from human plasma. HDL-like particles have certain distinct benefits, including desirable delivery due to their size, and uptake, due to cancer cells' increased need for cholesterol and other membrane components to sustain their rapid growth [147]. Such BMNPs also show potential for incorporation of other types of NPs, including AuNPs, Fe_3O_4, and QDs, for the purpose of prolonging circulation and reducing potential toxicity [148]. Nanovaccines have been constructed in this way, through chemical addition of antigens/adjuvants in the core or on the surface of these HDL-like NPs, as well as ligands for targeting or enabling of specific intracellular trafficking pathways [149]. Kuai et al. synthesized HDL nanodiscs for antigen/adjuvant co-delivery for immune response induction [150]. The $OVA_{257–264}$ SIINFEKL peptide antigen was tested along with CpG adjuvant, with positive *in vitro* and *in vivo* results, including high T cell activation measured by interferon (IFN)-γ ELISpot assays and tetramer staining, amongst other methods. These BMNPs also enhanced CD8 + T-cell tumor attack 41-fold *in vivo* compared to HDL-free formulations. Finally, the HDL nanodiscs were tested in combination with PD-L1 blockade, with an impressive 63% more tumor inhibition compared to the non-HDL delivered group, as well as prevention of occurrence upon subsequent tumor challenge [150]. This was quantified using immortalized immature dendritic cells (JAWSII) in C57BL/6 mice bearing B16 murine melanoma or MC38 murine colon adenocarcinoma tumors. The model was explored using melanoma and colon cancers, for ease of use with known "neoantigens". However, the immunotherapy modalities using neoantigens stand as proofs of concept, and can be similarly applied to other cancers, namely breast and cervical, of interest in this paper – the challenges in such cases being that neoantigens need to be defined, extracted, and purified first.

Lastly, biomimetic nanovaccine formulations have been tested in, and developed for, breast cancer therapy. In an exemplary study by Xiao et al. [151] membrane-functionalization is shown as a promising approach to cancer vaccination without the addition of an extra antigen. Biomimetic breast (4T1) cancer cell membranes, with antigenic feature intact, were used to coat PLGA nanoparticles loaded with the immunoadjuvant, imiquimod. They observed increased anti-tumor responses against 4T1 cells *in vitro*, as well as increased DC uptake and maturation. Repeated (3 times) administration of the above biomimetic nanovaccine established immune memory which reduced tumor growth and increased survival significantly. This is believed to be due to a reduction in Treg cell presence around the tumor, an increase in specific CD8 + T cell killing, and the presence of memory T cells in the spleen, achieved efficiently by particles bearing 4T1 membranes for both stealth and antigenic delivery. Moreover, the nanovaccine showed a strong stimulatory effect upon release of IL-12, causing memory T cells to secrete INF-γ and tumor necrosis factor (TNF)-α with further antitumor effects.

Biomimetic cervical cancer nanotherapy

Cervical cancer remains a danger to a large population, being the fourth most common neoplasia in females, globally [29,152]. Even in an age of accessible HPV vaccination (albeit preventative and not therapeutic) and with gold standard chemo- and radiotherapy, mean survival time is relatively short, necessitating the search for high-efficacy novel therapies with little or no effect on normal tissues. As mentioned above, biomimetic nanomedicines have the potential to bring researchers closer to these goals. Below, examples of BMNPs assessed for activity against cervical cancer are presented. All examples of these novel therapies applied in cervical cancer treatment were published since 2016; however, the majority are from the past two years, marking BMNPs as a true novelty in this area.

In vitro and in vivo experimental biomimetic cervical cancer nanotherapies

An excellent example of the capabilities of biomimetic nanomedicine was reported by Gao et al., who tested stem cell membrane-coated gelatin nanogels for targeted DOX delivery. They observed significant increases in circulation time compared to both free DOX and gelatin hydrogel-loaded DOX. In addition, endpoints including increased uptake and tumor reduction *in vitro* and *in vivo* showed improvement over the non-biomimetic formulations [153]. Another unique example within

cervical cancer involved the use of LDL-mimicking NPs coated with a neutral lipid and cholesterol bilayer, with a cholesterol core and recombinant targeted protein-PEG-folic acid (FA) chains, aiming to increase biocompatibility and trafficking of encapsulated paclitaxel towards tumor tissues, based on the increased demand for FA by rapidly dividing cancer cells. Uptake was heavily dependent on folate receptor expression. When endocytosed, folate receptors tend to follow clathrin and caveolae-mediated uptake pathways, but when these NPs were introduced, lysosomal evasion and endosomal escape were achieved *via* the pH-dependent fusogenic lipid used, releasing contents upon contact with lower endosomal pH. This tightly controlled release is pivotal to the success of BMNPs, which in this case showed the efficiency of drug delivery through rational design, drawing on multidisciplinary expertise in both formulation chemistry and biology [154]. It should be noted that the choice of lipid type in nanoparticle synthesis is key, for certain properties such as fusogenicity in this case. Lipid constituents and their uses, properties, and functions in lipid-based nanomedicine are summarized in a recent review by Fobian et al. [14].

As mentioned, PTT and PDT have also been explored using BMNPs. PDT was studied in cervical cancer context by Gao et al. using stimuli-responsive stem cell membrane camouflaged NIR nanoarchitectures combined with mesoporous silica NPs. The increase in targeting resulted in remarkable tumor growth inhibition and increased apoptosis and necrosis in the BMNP-treated tumor tissue [155]. PTT examples in literature include the use of Prussian blue NPs with stimuli-responsive elements and cell membrane coating, as well as tungsten sulfide sheets, and graphene oxide NPs coated with erythrocyte membranes. These achieved varying levels of improvement over the non-NP formulations, but overall, toxicity was reduced and delivery improved [117, 156,157]. The importance of the targeting effect of PTT-applied NPs is highlighted by the damaging and dose-limiting effects of PTT seen against normal tissues [158]. The principle exemplified above, of co-delivery of combinational therapeutics, has also been explored in the context of CRISPR and/or plasmid delivery. Noureddine et al. designed PEGylated cationic lipid-coated MSNs with the goal of efficient delivery of CRISPR-Cas9 machinery to tumors. A promising 70% of cargo was released intracellularly, which is an improvement, but the gene editing potential thereof did not match up to the current gold standard, CRISPRmax [159]. The authors report a biomimetic design in this case, but there were no biological materials added – it is thus assumed that they used "biomimetic" in reference to the lipid components added, which chemically resemble a cytoplasmic membrane bilayer.

The most compelling examples for the use of biomimetic nanotherapies were found in studies exploring combination therapies, delivering a multifunctional payload comprising multiple elements; thus, with more than one function. Huang et al. discuss an MSN functionalized with HeLa cervical cancer CM for delivery of ICG, the activity of which is hindered by poor pharmacokinetics. The MSNs were used to improve dispersion, loading efficiency, and biocompatibility, and HeLa membrane-functionalization was used to enable homologous HeLa cell-targeting. Increased accumulation in tumor tissue *in vivo* enhanced photoacoustic imaging quality compared with free ICG [160]. Xu et al. explored PLGA NPs functionalized with HeLa membrane for co-delivery of paclitaxel and siRNA to achieve knockdown of the oncogenic HPV E7 gene. These particles showed significant tumor growth reduction *in vivo*, compared to non-coated PLGA NPs, as well as siRNA-loaded PLGA NPs alone. An overview of the study design and key results is provided in Fig. 6a–d [26]. Such studies show potential for using patient-derived material to synthesize BMNPs for drug delivery or immune therapy, thereby leveraging a novel and more effective avenue of personalized medicine. However, many studies, the above being no exception, have used nude (athymic) mouse models, preventing researchers from commenting on the immunogenicity of these NPs. Thus, though these examples cover a diverse range of NP types, outcomes tend to be similar,

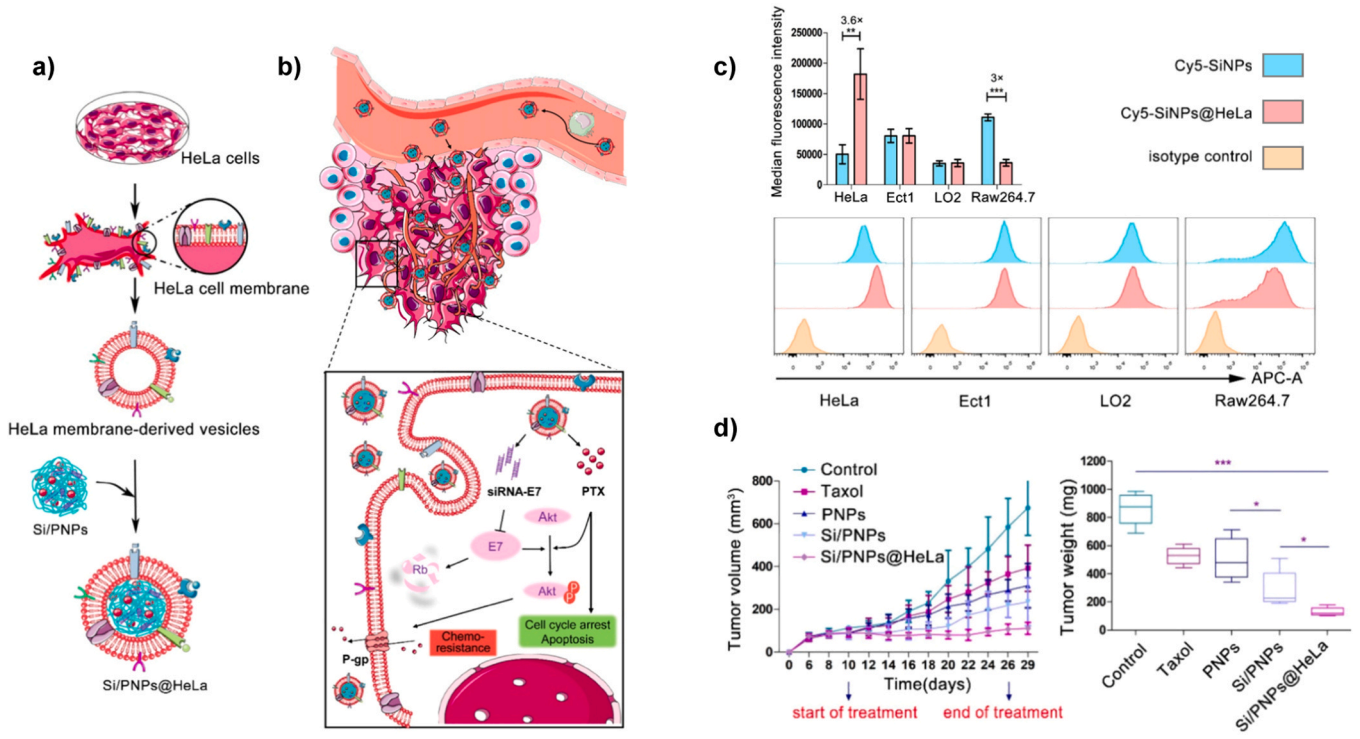

Fig. 6. Summary of the research by Xu et al. [26] including **a)** a schematic of the preparation steps involved, **b)** an overview and hypothesized mechanism of action of the biomimetic nanotherapeutic described and tested in this paper, **c)** increased uptake in four separate cell lines *in vitro* (median fluorescence intensity and histograms), and **d)** increased antitumor efficacy in vivo. licensed under CC BY 4.0 http://creativecommons.org/licenses/by-nc/4.0/.**Abbreviations**: Si/PNPs (small interfering RNA/Paclitaxel co-loaded poly-lactic-co-glycolic acid nanoparticles); Si/PNPs@HeLa (small interfering RNA/Paclitaxel co-loaded poly-lactic-co-glycolic acid nanoparticles fused with HeLa cell membrane extract).
(d) Adapted from Xu et al. [26].

and this fact highlights the importance of rational design in this field. There are several paths that may be taken to reach similar outcomes.

Biomimetic theranostics for cervical cancer

As for theranostic BMNPs in cervical cancer, Huang et al. investigated mMSNs loaded with the ICG, and cancer-cell membrane-functionalization for photoacoustic imaging. These modifications to ICG prolonged circulation and improved imaging in tumor-bearing mice in a manner selective towards homologous tumor tissue, compared to uncoated ICG. Moreover, membrane-coating significantly increased retention time over MSNs without membrane material [160]. This introduced imaging capabilities as well as therapeutic potential. A further theranostic by Wang et al. on carbon QDs functionalized with HeLa membranes. This proved to be a biocompatible method for sensitively imaging vitamin B12 in cell systems [161]. A more extensive list combined with breast cancer applications is given in Table 2.

Pharmacokinetic studies in cervical cancer

Of the few studies that have been conducted in the area of biomimetic NPs for cervical cancer, three give a clear picture of strengths to be gleaned through the use of this class of NPs. Fig. 7a–c highlights three *in vivo* studies which representatively show clear improvements over conventional therapies in clearance and biodistribution, in cervical cancer models. Briefly, Xiao et al. showed that membrane coating significantly increased retention capacity of the tested nanoparticles within the tumor, and prolonged circulation time [156]; Xu et al. showed significant tumor accumulation *in vivo* when comparing free drug with NPs, but the evasion of clearance was significant in the cell-membrane-targeted variants [26], and Gao et al. tested stem-cell membrane-camouflaged gelatin nanogels, which showed increased circulation time compared to uncoated gelatin [153]. Overall, these studies demonstrate BMNP-mediated prolongation of circulation and tumor accumulation, shown by fluorescent whole-body imaging of mice and drawn plasma at longer timepoints. The importance of these findings is evident in the comparisons made within the shown experiments. Each study investigated formulations with similar nanoparticle cores, and added elements one-at-a-time to isolate the effects caused within that experimental group, and conclusively compare these effects. This is a common and important part of experimental design in studies involving experimental nanoparticles. These studies were also summarized in Table 3, in lieu of clinical studies, of which there are none for cervical cancer.

Biomimetic nanovaccines and immune therapies in cervical cancer

HPV-related vaccination and immune therapy. Cervical cancer is one of the few cancers displaying a causative relationship with a virus: HPV, more specifically; 70% of cases globally are caused by high-risk (hr) HPV types 16 and 18. This remains a significant cause of mortality, especially in developing countries, maintaining HPV-related cervical cancer elimination as a global priority for the WHO [172]. Though vaccination does offer significant prophylactic protection from cervical cancer, there is growing resistance to vaccination worldwide, and vaccination in developing countries continues to lag behind more developed countries. Both as a cancer with non-self-DNA integrated into its genome, and as one with possible chemotherapy resistance [173], cervical cancer is a prime candidate for immunotherapies, which are already clinically indicated in cases where the PD-1/PD-L1 axis is of use in tumor reduction [174,175].

An innovative example, and the only of its kind using BMNPs in literature was published by Xu et al. and is summarized in Fig. 7b above. In this study, targeted biomimetic nanomedicine is combined with siRNA against HPV oncoprotein E7, and paclitaxel co-delivery, for a significant and efficient synergistic anti-tumor effect [26]. Nanotherapies without biomimetic elements have also been explored in similar ways for treatment or therapeutic vaccination of HPV-related cancers. These are presented here as an exploration into the potential contained within nanomedicine, which could be applied in biomimetic nanomedicine with great benefit. These are summarized in comprehensive reviews by Pan et al. [176]. and Zhou et al. [43]. A shining example of this is the lipid-based HPV vaccine, PDS0101, comprising HPV16 peptides within a cationic liposome, which could promote the infiltration of CD8 + T cells [177]. Smalley Rumfield et al. modified this formulation, adding two immunomodulators, the first (Bintrafusp alfa) comprising fragments of transforming growth factor receptor (TGFβR) fused to an anti-PD-L1 monoclonal antibody, and the other promoting Th1 cell-mediated induction of inflammation and delivering IL-12 [178]. This combination of checkpoint inhibition with the activities of TGFβ and pro-inflammatory IL-12 increased the clonal expansion of T cells, thus inducing a potent anticancer outcome.

Apart from this, DNA and mRNA vaccines form an important branch of immune therapy, and both tend to rely on nanomedicine for delivery, given the chemical properties of nucleic acids. An excellent and recent example of this is the use of PEGylated LNPs for delivery of the mRNA vaccine against COVID-19 [179]. The negative charges of DNA and mRNA can be complexed with cationic lipids to form stable, injectable formulations, and is already established in cervical cancer [43]. For example, HPV E7 antigen-encoding mRNA was coupled with cationic liposome vectors [180], which were presented using DCs *in vivo*, bringing about significant CD8 + T cell responses leading to complete removal of tumors. These were co-administered with anti PD-L1 checkpoint inhibitors for added tumor reduction, as the lipid-RNA complex was shown to resensitize checkpoint inhibition-refractory tumors to these therapies [181].

One of the challenges for successful immune therapy of HPV, and most cancers, is the ongoing generation of subclones of the original tumor, each with new immune-avoidance strategies, mutations, variations in immune-cell constituents in the TME, and loss of antigenicity [14]. Combinational approaches including antigen-specific and non-specific immune therapy elements will be required for control of these tumors [182]. Furthermore, meaningful immune therapy models are few, especially when the subject of a study is a human cancer with specific nuances and pivotal characteristics which cannot be meaningfully replicated or emulated in animal models, as is the case with cervical cancer and HPV [43]. BMNPs add value in these areas through targeted delivery, protection of immunotherapeutic cargo (antibodies, or diverse types of vaccines), and personalized medicine approaches, where particles may be synthesized with homogenous patient material for improved delivery and immune response modulation.

Artificial antigen presentation and immune mimicry. An interesting example of BMNP functionalization is APC mimicry, achieved by artificial APCs (aAPCs). These have no direct action on the tumor cells; rather, exist to prime phagocytes and T cells for specific targeting and prolonged activity [183]. aAPCs are a viable example of functional biomimicry. In nature, this has been around for centuries in the form of archaeosomes, the original natural liposomes produced by the unicellular, non-nucleated, organelle-lacking prokaryotes, known as archaea [184]. These have been harnessed in recent studies to stimulate DCs toward antigen presentation of HPV16 L1/E6/E7 protein fragments, while also being useful as adjuvants and delivery platforms [185]. However, there is a need for further optimization of a number of parameters, including surface decorations, bioactive agent co-delivery, and exact physicochemical parameters. Synthetic lymphoid organs have also been explored, which are 3D nanomaterial scaffolds used for the modulation or bolstering of desired immune responses in an engineered and controllable manner [186].

A final form of biomimicry is the use of cellular ligands for targeted delivery or in some cases, therapeutic effect. This has been explored in many ways [14], including the use of monoclonal antibodies or

Table 2
Theranostic applications of biomimetic nanoparticles within breast and cervical cancer. Abbreviations; C QDs (Carbon quantum dots); CDAuNs (coated surface of DOX-incorporated AuNs) ICNP (iron carbide nanoparticles); MPCM-AuNSs (Macrophage cell membrane camouflaged gold nanoshells); MRI (magnetic resonance imaging); NIR (near-infrared); NP (nanoparticle); PA (photoacoustic); PEG (polyethylene glycol); PLGA (poly(lactic-co-glycolic acid) nanoparticles); RBC-MNs (red blood cell membrane-functionalized magnetic nanoparticles); PDT (photodynamic therapy); PTT (photothermal therapy) SPN (semiconducting polymer nanoparticle).

Biomimetic material	Organic material					Inorganic material					References (respectively)
	Material	Carrier	Theranostic application	Cell line	In vivo outcome	Material	Carrier	Theranostic application	Cell line	In vivo outcome	
Erythrocyte	PEG	Nano-cage	NIR	4T1	Significant blood retention and anti-tumor efficacy without any damage to healthy organs	Fe3O4	@RBC-MNs	MRI & PTT	MCF-7	Remarkable blood circulation and desired passive EPR effect strong enough to even compensate the lack of magnetic field with an excellent anti-tumor PTT outcome	[162,163]
	PCL-PEG-PCL (PCEC)	NP	NIR	MCF-7	Improved anti-tumor efficacy	Prussian blue NPs	NP		MDA-MB231	Enhanced blood circulation, tumor accumulation	[164,165]
	PEG-b-PDLLA	NP	PDT	HeLa	Target accumulation with safe treatment	GOQDs	NP	PTT	Erythrocytes	Inhibited tumor growth in combination of chemo-or photothermal therapy	[117,166]
	(TMB)-copper peroxide (CuO2)@ (PLGA)@ (RBCM) (TCPR)	NP	PTT/PA	4T1	Significant suppressed tumor growth after 10 min laser irradiation with excellent therapeutic efficacy	WS2	Nano-sheet	PTT	Erythrocytes	Effective prolongation of blood circulation time specifically accumulate in the tumor site	[157,167]
Platelet	PLGA	NP	PDT	4T1	Decrease in average tumor size in the first four days	Fe3O4	PLT-MN NPs	PTT & MRI	–	Enhanced targeting resulting in improved PTT effects	[123,168]
	PLGA	PNP	PTT	MCF-7 & MDA-MB231	Improved the elimination half-life of PLGA NP						[120]
Cancer cell membrane	CC-UCNPs	NP	NIR	MDA-MB231	98.9% and 98.5% inhibited rates of the tumor size and metastatic nodules	CDAuNs	Nano-cage	PTT	4T1	Accumulation in tumor tissue with a low density in liver and spleen	[169,170]
	PLGA	ICNPs	(NIR)-FL/PA	MCF-7	Promotion of tumor killing and high accumulation	Au@Pt-M-NPs	NPs	PTT	HeLa	Promotion of efficacy of NP & enhancement of survival	[77,78]
	SPN	AF-SPN	PA & PDT	–	Tumor accumulation marginally higher than non-targeting uSPN.						[113]
						C QDs	NP	Fluorescent imaging	HeLa	Increased efficacy with higher accumulation	[161]
						MSN	NP	PA	HeLa	Specifically accumulated into the cervical tumor, which result in the homologous targeting ability.	[160]
Macrophage	MPCM-AuNSs	NP	NIR	4T1	Significantly increased blood retention time						[171]
	DOX-QDs-Lip@M	Lipo-some	QD	4T1 & RAW264.7	Targeted actively metastatic lung tissue and increased the drug accumulation with no change of body weight						[129]
Stem cells	MSN	NP	PDT	Stem cells	Increased tumor growth inhibition with no change in body weight						[155]
Hybrid	Prussian blue NPs	NP	PTT	HeLa + erythrocyte	With higher accumulation in tumor tissue						[156]

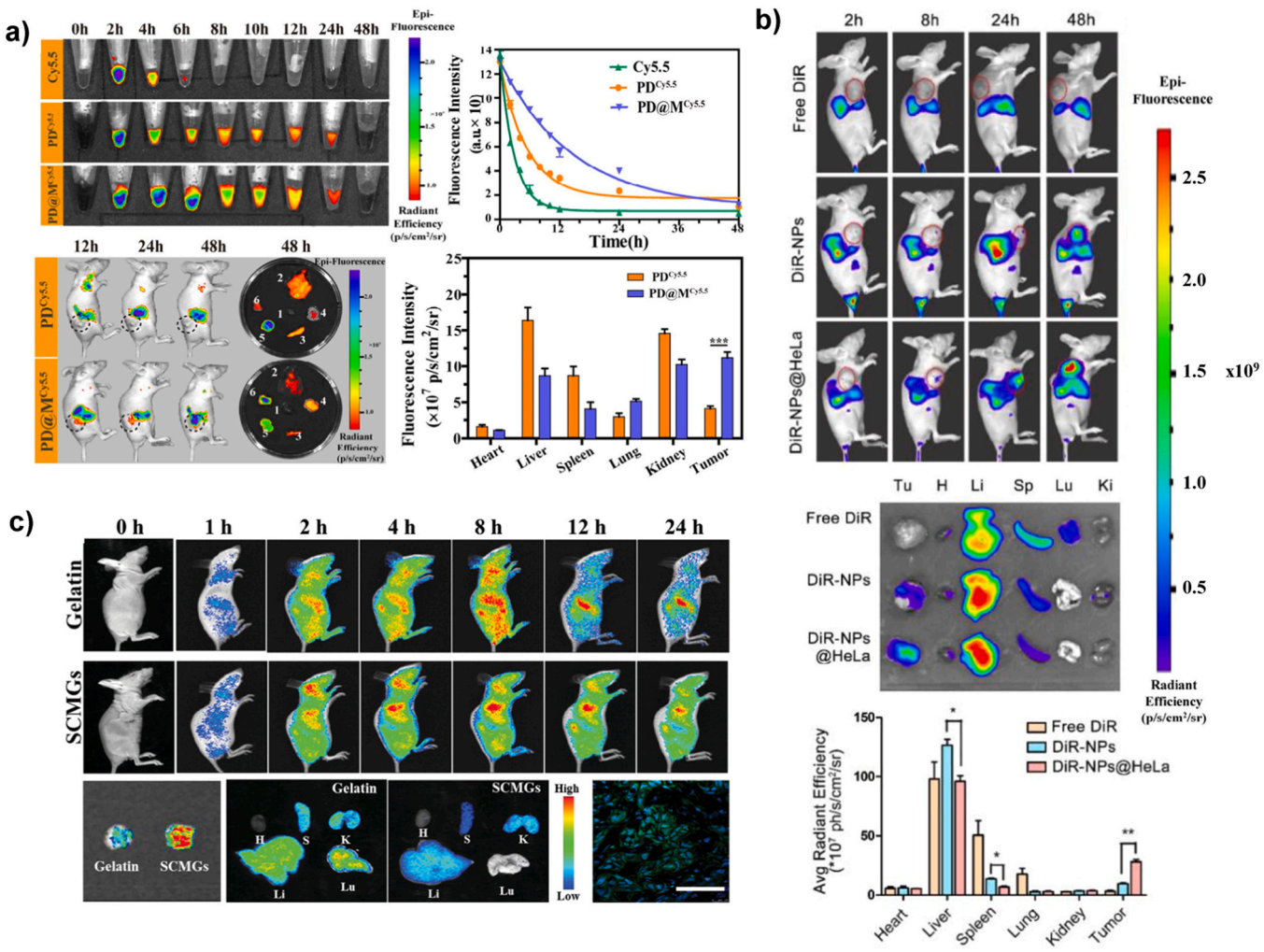

Fig. 7. Compilation of selected *in vivo* clearance and biodistribution studies for cervical cancer. **a)** Biodistribution and pharmacokinetics studies show that the cell-membrane-functionalized nanoparticles improved not only circulation, but also accumulation in the tumor, shown by plasma fluorescence and whole-body imaging of mice. Membrane coating significantly increased tumor retention and circulation time as evidenced by high presence of NPs in drawn plasma, even after 24 h [156]. **b)** In vivo studies showed significant tumor accumulation with NPs, but the effect was especially pronounced in the cell-membrane-targeted variants. **c)** Stem-cell membrane-camouflaged gelatin nanogels showed increased circulation time over gelatin gels alone. © 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. **Abbreviations**: Cy5.5 (sulfocyanine5.5); PD$^{Cy5.5}$ (Prussian blue-polydopamine-Cy5.5); PD@M$^{Cy5.5}$ (PD$^{Cy5.5}$-cell membrane); SCMGs (stem cell membrane-coated gelatin nanogels); DiR (1,1′-dioctadecyl-3,3,3′,3′-tetramethylindotricarbocyanine iodide); DiR-NPs (DiR-nanoparticles); DiR-NPs@HeLa (DiR-nanoparticles-HeLa cell membrane); T (tumor); H (heart); Li (liver); Sp (spleen); Lu (lung); Ki (kidney).
(a) Reprinted from Journal of Controlled Release, vol 339, Xiao C, Tong C, Fan J, Wang Z, Xie Q, Long Y, et al., Biomimetic nanoparticles loading with gamabutolin-indomethacin for chemo/photothermal therapy of cervical cancer and anti-inflammation, Pages 259–73, copyright 2021 with permission from Elsevier. (b) Reproduced with permission from Gao et al. [155]. (c) Adapted from Xu et al. [26], licensed under CC BY 4.0 http://creativecommons.org/licenses/by-nc/4.0/.

fragments thereof, such as anti-PD-L1, PD-1, HER-2, CTLA-4 and many others on the surfaces of nanomedicines [24]. Studies have also shown promising results using T cell receptor fragments designed using a phage display library against HLA-bound tumor specific antigen for therapeutic effect in certain cancers [23,187]. Other mimicry of immune cells exists, including the use of leukosomes [188] and a range of other BMNPs with immune-cell membranes, with various levels of structural and functional mimicry, and varying success. These are expounded in extensive reviews by Oroojalian et al. [72]. and Sushnitha et al. [189]. The uses thereof, underlying biology, and the ever-present hurdles which exist within the preparation and extraction of these elements in a function-preserving, pure, and reproducible way, are discussed in detail.

Perspectives on biomimetic nanomedicine for cervical cancer therapy

Considerations for marketability of nanoparticles

Amid the hopeful and convincing outcomes of the cited research above, Metselaar and Lammers have taken a sobering look at the nanomedicine landscape as a whole. They mention the following five snares related to the market success of nanomedicines (which includes BMNPs): 1; commercial feasibility, 2; clinical development feasibility, 3; preclinical efficacy for desired clinical outcome, 4; preclinical toxicity, and 5; management of chemistry, manufacturing, and quality control [190]. Contained within these five areas are all of the barriers hindering the marketability of the many promising nanomedical innovations seen in preclinical studies. Particular attention, in our opinion, should be brought upon points one, two, and four. In points one and two, the scale-up and actual benefit to patients' lives are called into question.

Table 3
New clinical trials for innovations in the field of nanomedicine since January 2020 are outlined for breast and cervical cancer. **Abbreviations**: CNP (carbon nanoparticle); DOX (doxorubicin); ICG (indocyanine green); Nab-paclitaxel (albumin-NP-bound paclitaxel); PTX (paclitaxel); SPION (superparamagnetic iron oxide nanocrystals); LNP, lipid nanoparticle; mRNA, messenger ribonucleic acid; PD-1, programmed death protein 1.

Cancer type	Posted	Nanomaterial	Study premise	NCT ref #	Status
Breast cancer	2023	SPION	SPION used as tracer to mark sentinel nodes	NCT05985551	Active, not recruiting
	2023	LNP	LNPs encapsulating mRNA results in uptake and selective expression by myeloid cells *in vivo*, thus delivering MT-302, a TROP2-targeting *in vivo* chimeric antigen receptor for immune response engagement.	NCT05969041	Recruiting
	2022	SPION	SPION (MagTrace®) used as an alternate liquid tracer to mark sentinel nodes	NCT05625698	Recruiting
	2022	Nab-PTX	Combination therapy (+ PD-1 inhibitor or other mAb therapy)	NCT05422794	Not yet recruiting
	2022, 2021, 2021	SPION or CNP	Sentinel lymph node detection and imaging	NCT05359783, NCT05161507, NCT04951245	Active, not recruiting; recruiting; completed
	2022, 2020	Nab-PTX	Personalized medicine (genetic signatures or using of patient material)	NCT05238831, NCT04216472	Not yet recruiting; active, not recruiting
	2021	Nab-PTX	Wearables (Tumor-treating fields) generating therapeutic electric signals, combined with atezolizumab, carbozatinib, and Nab-PTX.	NCT05092373	Recruiting
	2021	C'Dots (Silica NPs)	C'Dots combined with experimental drug, payload and folic acid-based targeting moieties	NCT05001282	Recruiting
	2021	Gadolinium NPs	Gd NPs investigated assistance of x-ray guided radiation	NCT04899908	Recruiting
	2020	Nano-irinotecan	Nanosized irinotecan formulation investigated	NCT04640480	Recruiting
Breast or cervical cancer	2023	Carbon NP-Loaded Iron [CNSI-Fe(II)]	CNSI-Fe(II) shows promise as an innovative tumor therapeutic agent due to its unique properties of ferroptosis. This study will evaluate safety and most suitable dose.	NCT06048367	Recruiting
Cervical cancer	2021	Carbon NPs	ICG with CNPs for imaging sentinel lymph nodes	NCT05167149	Unknown

Basic researchers may develop tunnel vision regarding efficacy and safety, whereas in the industry, true benefits such as convenience (frequency of dosing, route of administration) and comfort (fewer side effects and lower toxicity) are of great importance and prevent the progression of novel formulations into the clinic. Alongside this is the notion among researchers to design something which will yield maximal experimental effect. This is sufficient in some respects, but in others, dismisses scalability, quality control, and feasibility, relying on the superior quality of the small-batch product reported upon for academic publications. This notion should be taken alongside thoughts of scalability from the beginning of the development process, such that a potential product may be developed with that in mind [190]. Point four alludes to a more technical point, and that is the frequent high toxicity observed once the product advances from preclinical research. The best way to address this is better and more predictive preclinical toxicity models. Innovations in *in vitro* models are occurring every day, but for now, the nanomedicine research community continues to rely on animal models [191]. Adding biomimetic elements to nanomedicines will certainly complicate the clinical development thereof, owing to sterility and ethical considerations when using biologically derived material. This, as well as significantly more complicated synthesis methodologies and quality control points, will surely make BMNPs' road to the clinic a long and windy one.

Concluding remarks

From the works reviewed in this article, it is clear that there is scope for meaningful growth in the area of biomimetic nanomedicine for cervical cancer therapy. Novel therapies are needed, especially considering the untapped potential of targeting viral proteins involved in the oncogenesis of this cancer. Further to this, applications in delivery and immune therapy which combine vaccination elements with drug delivery and immune modulatory agents in a manner resilient to pharmacokinetic co-administration complexities, would be of great benefit [43]. However, this is only half of the battle won.

Delivery to target sites in a selective manner is being achieved frequently and reproducibly, but not to the extent necessary for decreasing toxicity in other tissues. That is a common problem with targeted therapies, whereby targets themselves are not suitably present in target tissues, or indeed, absent in off-target (normal) tissues [14]. This is known as on-target off tumor toxicity, most common in chimeric antigen receptor (CAR) T cell therapy [192], but also prevalent in diverse targeted nano- or other therapies. A further consideration within targeting is the subcellular localization of nanoparticles. Lysosomal evasion and endosomal escape are of key importance to maintain biological activity within tissues of interest, by avoiding degradation [193]. In some examples presented in this paper, several of these challenges have been overcome through innovation and rational design, yielding the desired biological response.

The needs in the clinic for more precisely targeted delivery mechanisms and sustained or controlled release formulations are increasingly dire, especially in an era where quality of life and patient comfort are beginning to be prioritized more than merely survival. That, we believe, is the greatest strength of biomimetic nanomedicine: its utility as a platform which should be widely applied to existing and efficacious therapies, for optimized delivery of therapies [194]. Several studies have focused on combinational therapies for a range of cancers; however, not often with nanomedicine; even less so with biomimetic nanomedicine [43,195]. Further, where nanomedicine has added immense value to this field, and promises to continue doing so, biomimetic formulations stand to improve on that, as the balance between tissue and cell recognition, and maintaining stealth is very delicate. This review has summarized the ways in which that occurs, drawing on the wealth of available research conducted for breast cancer, with the hope of stimulating innovation and driving discovery in this young and cutting-edge field, for more efficacious and safer cervical cancer therapy.

CRediT authorship contribution statement

L. Farhoudi, S. Fobian, A. L. Oei, M. Amin, M. R. Jaafari, & T. L. M. ten Hagen: The authors declare that there is no conflict of interest in the context of this paper. All authors have read and consent to the publication of the entirety of this work. LF – Conceptualization of paper and writing of manuscript. SF – Conceptualization and writing of manuscript, editing, and compiling of written sections. TtH, MA, AO, MJ – Expert review and editing of manuscript. LF and SF made equal contributions to this paper and agree to sharing first authorship on it.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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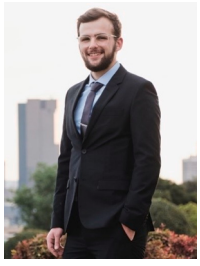

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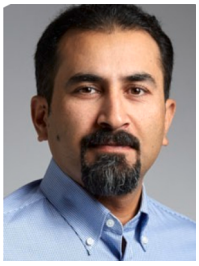

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Assoc. prof dr Timo ten Hagen is a principal investigator and researcher specializing in cancer therapy and nanotechnology. He is particularly interested in improving tumor therapy through the manipulation of the tumor microenvironment and the use of lipid-based nanocarrier delivery systems. Timo's research also focuses on understanding the individual characteristics of tumor cells that determine progression and clinical outcome, including cell migratory and survival capacity and evasion of local immunological processes. Using his expertise in nanotechnology and immunology, Timo is investigating the use of immunity modulation and tumor immunotherapy for the treatment of solid cancers, with a focus on melanoma, cervical cancer, and breast cancer.