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REVIEW

Nanomedicine applications in women's health: state of the art

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Abstract: State-of-the-art applications of nanomedicine have the potential to revolutionize the diagnosis, prevention, and treatment of a range of conditions and diseases affecting women's health. In this review, we provide a synopsis of potential applications of nanomedicine in some of the most dominant fields of women's health: mental health, sexual health, reproductive medicine, oncology, menopause-related conditions and dementia. We explore published studies arising from in vitro and in vivo experiments, and clinical trials where available, to reveal novel and highly promising therapeutic applications of nanomedicine in these fields. For the first time, we summarize the growing body of evidence relating to the use of nanomaterials as experimental tools for the detection, prevention, and treatment of significant diseases and conditions across the life course of a cisgender woman, from puberty to menopause; revealing the far-reaching and desirable theoretical impact of nanomedicine across different medical disciplines. We also present an overview of potential concerns regarding the therapeutic applications of nanomedicine and the factors currently restricting the growth of applied nanomedicine.

Keywords: nanomedicine, mental health, sexual health, reproductive medicine, oncology, menopause, dementia

Introduction

Nanomedicine is the application of nanotechnology in the field of medicine with a view to enhancing the diagnosis and treatment of various diseases. Nanotechnology is already involved in a range of biomedical applications including drug and vaccine delivery, diagnostic imaging, nanosensor diagnostics, nano-enabled therapies, and tissue engineering.[1–3] Across the UK and the European Union, a growing recognition of the specific health care requirements of women has resulted in the proposed organizational changes in the provision of health care, focusing predominantly on a life course approach to women's health care.[4–7] However, the predictable long-term health care needs of women demand greater biomedical and translational research to develop the diagnostic tools and treatments necessary to improve the care and well-being of women. Although cancer has been the predominant focus of research in the field of nanomedicine,[8] there is an increasing awareness and exploration of the potential application of nanomedicine to noncancerous pathologies. As our understanding of the benefits of nanomaterial-based agents and diagnostics continues to grow in terms of selectivity, sensitivity, affinity, and detection limits, there is a widespread anticipation that nanotechnology will play an increasing role in women's health.[1,9–18] This review explores the selection of potential nanomedicine applications in women's health, from puberty to menopause in cisgender women, including mental, sexual, reproductive, cancer, and menopause-related health care (Figure 1; Tables 1 and 2). We also address

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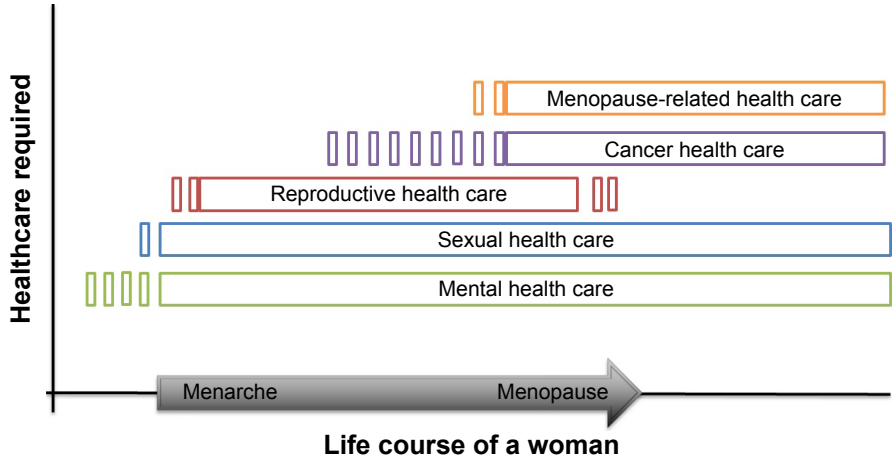

Figure 1 A representative graph showing the significant and predictable health care needs across the life course of a woman.

how this exciting technology might be deployed in early-onset dementia health care. These disciplines align directly to the key components of the World Health Organization's "Top Ten Issues for Women's Health." Specifically, we highlight the potential of nanomedicine to revolutionize health care throughout the life course of women and discuss the challenges that might restrict the widespread application of these nanotechnologies to clinical medicine.

Table 1 The applications of nanoparticles in women's health care: mental health and sexual health care trials and clinical studies

Sector	Speciality	Application	References
Mental health care	Therapeutics	Enhanced drug delivery and release mechanisms	Ashok et al,[40] Leyva-Gómez et al,[41] Kim et al,[42] Jana et al,[43] Zhou et al,[47] Shah et al[48]
		Increasing bioavailability of drugs	Gao et al,[52] Yan et al[53]
		Alternative drug delivery systems	Huang et al,[57] Wei et al,[58] Grabrucker et al[59]
Sexual health care	Fertility	Nanoparticles with antifertility capability	Gaurav et al,[61] Liu et al,[62] Jha et al,[66] Marfatia et al[70]
	Sexually transmitted diseases	Prevention of infection	Fayaz et al,[71] Caron et al,[81] Kovarova et al[82]
		Detection of infection	Lee et al,[83] Singh et al,[95] Singh et al,[96] Yang et al,[105] Tang et al,[106] Beeghly-Fadiel et al[119]
		Treatment of infection	Rauta et al,[97] Mishra et al,[101]
		Vaccination/ immunity against infection	Fairley et al,[98] Dixit et al,[99] Cambridge et al,[100] Yilma et al,[102] Liu et al,[94] Villa et al[87]

Table 2 The applications of nanoparticles in women's health care: reproductive health care, cancer, and menopause care trials and clinical studies

Sector	Specialty	Application	References
Reproductive health care	Endometriosis	Imaging of endometriosis	Hue et al,[110] Zhang et al[111]
		Delivering gene therapies to target tissues	Zhao et al,[112] Chaudhury et al[113]
	Uterine fibroids	Targeting delivery of antitumor drugs	Jiang et al,[114] Ali et al[115]
Cancer health care	Tumor imaging	Magnetic resonance imaging (MRI)	Zhang et al,[125] Yang et al[213]
		Computed tomography (CT)	Zhou et al[126]
	Cancer screening	Detection of malignant cells in tissue samples	Liu et al,[130] Jo et al,[132] Palantavida et al[129]
	Therapeutics	Receptor specific targeting	Zhang et al,[142] Yu et al,[156] Yang et al[150]
		Sensitization of malignant cells	Yang et al,[121] Liang et al[143]
		Manipulation of cellular pathways	Yang et al,[150] Zhang et al[153]
		Overcoming drug resistance	Peetla et al,[146] Roberts et al,[147] Wang and Jia[149]
Menopause-related health care	Declining estrogen	Improvements for hormone therapy	Valenzuela and Simon,[171] Simon[170]
	Osteoporosis	Manipulation of osteogenesis activity	Hwang et al,[178] Psarros et al[179]
		Bone-specific drug delivery	Khajuria et al[176]
	Cardiovascular disease	Reduction of LDL levels	Xiao et al[183]
		Targeting atherosclerotic growth/inflammation	Chono et al,[181] Chnari et al,[182] Winter et al[184]

Mental health care

Mental health is a significant and growing issue in women's health. Analysis of the four Adult Psychiatric Morbidity Surveys published since 1993 has demonstrated the growing burden of common mental health disorders in women's health care and revealed a gender gap in common mental health disorders.[19] Analysis of these surveys indicated that in England, 20.7% of women had a common mental health disorder, a figure which was 7.5% higher than that in men. Furthermore, since 2000, the prevalence of common mental health disorders in women has continued to increase, yet has remained stable, for the most part, in men. Although women are found to be more likely to receive treatment than men, the antidepressants commonly used in the treatment of common mental health disorders such as anxiety and depression are not consistently efficacious.

An individual's gender has been identified as a factor affecting treatment response.[20] Studies in mice have shown that greater neuronal activation arises in response to an acute citalopram injection in male mice, than in female mice or gonadectomized male mice, suggesting the possible influence of gonadal hormones upon the complex interactions between serotonin and neural circuits that mediate the hypothalamic–pituitary–adrenal stress axis.[21] It was proposed that the regulation of androgens might dampen and modulate the activation of the stress pathway, which could contribute to the greater vulnerability of women to stress-related affective disorders. In light of the possible inherent gender gap in common mental health disorders, it is vital that efforts are made to increase the efficacy of the existing pharmacological treatments to improve the well-being of women. Both pharmacological and neurobiological factors have been implicated in antidepressant resistance.[22]

The function of the blood–brain barrier is believed to be a significant factor affecting antidepressant resistance.[23] The blood–brain barrier contributes to brain homeostasis and features drug efflux transporters of the ATP-binding cassette gene family including P-glycoprotein (P-gp).[24] Many antidepressants are substrates of P-gp and therefore exhibit reduced penetration into the brain.[22] Although not all antidepressants are subject to the same degree of limitation to brain penetration by P-gp in vivo,[25–28] several single-nucleotide polymorphisms of the *ABCB1* gene have been linked to reduced levels of clinical response to antidepressants,[29–33] and a poorer tolerance profile.[34–36] However, several studies have failed to reproduce these results.[37–39] The proposed involvement of P-gp in antidepressant resistance indicates that P-gp may be systematically targeted and inhibited by particular drug delivery systems, enabling more of the drug to cross the blood–brain barrier, thus establishing greater concentrations at the site of action.[14]

Serotonin–norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs), in addition to the other commonly prescribed benzodiazepine class of anxiolytics, are orally administered in the majority of cases of common mental health disorders. Therefore, these drugs are also limited by factors such as low drug aqueous solubility, food–drug interactions, high hepatic first-pass metabolism effects, and short half-lives. In addition, poor compliance is a common cause of anxiolytic resistance in all three classes. Promising in vitro and in vivo studies offer the hope that nanomedicine could overcome many of these causes of low bioavailability and drug resistance.[14]

The initial studies involving benzodiazepine drug nanocarriers have been positive. Lipid-based micelles have proved to be successful at improving the aqueous solubility of diazepam in vitro by 2.3- to 6-fold. Furthermore, solid lipid nanoparticles (NPs) carrying clonazepam demonstrate enhanced blood–brain barrier permeability and efficacy at lower doses than required by the pure form of the drug revealing their potential as oral delivery systems for drugs with poor water solubility.[14,40,41] In addition, in vivo, clonazepam-loaded polymeric NPs demonstrated sustained drug release exceeding 80 hours in the presence of the enzyme dextranase, subject to the pH of the release medium being appropriate, and alprazolam-loaded polymeric NPs have also demonstrated sustained drug release over a 24-hour period in vitro.[42,43] Moreover, liposomes have been utilized in vivo to encapsulate midazolam, successfully increasing the oral bioavailability of the drug by 3.6-fold relative to the pure form of the drug.[14,44] These examples provide clear evidence of the potential of nanoscale drug delivery systems to improve the physiochemical properties of benzodiazepine drugs, ultimately increasing the fraction of the orally administered drugs that reach the systemic circulation. They also suggest the possibility of benzodiazepine depots, which could maintain a constant drug concentration for a prolonged and predetermined period of time with minimum side effects, offering hope for the safer prescription of drugs with improved patient compliance.

Other studies that have been conducted in nanocarriers loaded with SNRIs and SSRIs have proved similarly promising results. Solid lipid NPs carrying duloxetine HCl have demonstrated excellent stability in acidic media and enhanced

pharmacodynamic properties in vivo. Likewise, duloxetine HCl-loaded mesoporous silica NPs exhibited sustained drug release during in vitro studies.[45,46] Furthermore, solid lipid NPs carrying venlafaxine showed a 1.45-fold increase in oral bioavailability relative to the pure drug. The drug concentrations in the brain were also increased significantly when administered through the solid lipid nanocarrier, suggesting a reduction in P-gp-mediated efflux of the drug.[14,47] Moreover, venlafaxine hydrochloride (VHL)-loaded chitosan NPs have shown steady release in vitro, and VHL-loaded dendrimers demonstrated sustained drug release in vitro.[48,49] Studies of fluoxetine HCl cocrystals, fluoxetine HCl with benzoic, succinic, and fumaric acid cocrystal formers in the same crystal lattice, further revealed that the solubility of the cocrystal formers determined the aqueous solubility of the cocrystals. This has the potential to inform the development of optimal cocrystal engineering for maximal bioavailability in future.[14,50] As with the benzodiazepine class of drugs described in the preceding paragraph, this initial preclinical evidence indicates that SNRIs and SSRIs may benefit from nanoscale drug delivery systems that can provide opportunities for enhanced oral bioavailability and the development of drug depots. In addition, these studies demonstrate that greater concentrations of SSRIs and SNRIs may be established in the brain by reducing P-gp-mediated efflux and by preventing the upregulation of P-gp expression through the use of drug delivery systems.

Nanomedicine also offers significant potential to improve the efficacy of alternative and novel therapies, administration techniques, and augmentation strategies. For example, solid lipid NPs were successfully demonstrated to increase the bioavailability of buspirone HCl by 2.35-fold. This phenomenon was attributed to reduced hepatic first-pass metabolism, which may ultimately enhance the efficacy and diminish the interindividual variability associated with this novel anxiolytic which is sometimes used to augment antidepressants.[14,51] In addition, in vitro studies of amitriptyline HCl nanocrystals suggested that the development of nanocrystals may offer a means to increase the rate and extent of drug dissolution.[14,52] Although tricyclic antidepressants such as amitriptyline HCl have been largely superseded by SNRIs and SSRIs, this study demonstrated the potential of nanocrystals to enhance the physiochemical properties of the drug for application in suitable, antidepressant-resistant, patients. Furthermore, agomelatine cocrystals enhanced aqueous solubility by up to 4.7-fold relative to the pure form of the drug, which is a novel melatonergic antidepressant with a favorable side effect profile relative to the more commonly used antidepressants.[14,53]

A study conducted on the antidepressant effects of the curcumin/solid lipid NP dexanabinol (Cur/SLNs-HU-211) dual-drug NPs for the treatment of major depression utilized corticosterone-induced cellular and animal models of major depression.[54] Cur/SLNs-HU-211 showed superior antidepressant activity compared to HU-211, Cur, and Cur/SLNs in vitro and in vivo.[54] Although curcumin remains a controversial and poorly researched alternative form of therapy, this study is suggestive of the potential of nanomedicine to overcome pitfalls that can curtail experimental leads for novel antidepressants; in the case of curcumin, potentially improving the normally unstable, reactive, and non-bioavailable compound. A superior antidepressant-like effect of trefoil factor 3 (TFF3) loaded into negatively charged liposomes was observed in animal models of depression. These findings indicated the potential of developing TFF3 liposomes as a potential antidepressant drug for acute systemic administration. In this way, the neuropeptide TFF3 may be enhanced by nanomedicine to potentially improve the efficacy of clinically used antidepressants.[55] Moreover, cRGD-modified liposomes produced a heightened antidepressant response of TFF3 by increasing the brain distribution of TFF3. It is now necessary to conduct further research on the efficacy and safety of using cyclic Arg-Gly-Asp (cRGD) coupled with liposomes as a drug delivery system targeted at the brain. This may enable exploration of the potential use of cRGDL-TFF3 for the treatment of common mental health disorders.[56]

Nanomedicine may also contribute to improving alternative drug administration methods. An animal study highlighted the potential of micro-emulsions to be utilized as a drug delivery system for the transdermal administration of citalopram. This study indicated that a formulation, containing 3% citalopram within an application area of 3.46 cm^2, was capable of reaching the minimum effective therapeutic concentration with no significant local side effects.[57] In addition, curcumin didecanoate CurDD nanosuspensions have been proposed as an alternative long-acting intramuscular injectable antidepressant through the sustained delivery of curcumin.[58]

In another study, novel biodegradable NPs, composed of poly-lactide-co-glycolide (PLGA) conjugated with glycopeptides, were shown to be capable of crossing the blood–brain barrier and were able to deliver Zn^{2+} ions, which may permit their application in the augmentation of antidepressant treatments.[59]

In summary, the clinical application of nanocarrier systems in mental health remains a speculative, but tantalizing, possibility at this time. The studies presented here illustrate the

positive theoretical impact of their translation into clinical medicine. Nanomedicine may offer the potential to improve the efficacy of conventional pharmaceuticals that are currently limited by antidepressant resistance, by enhancing the bioavailability and pharmacokinetics, as well as facilitating antidepressant augmentation. Furthermore, it may facilitate the development of novel therapies for use in the treatment of common mental health disorders. In addition, it may improve the range of drug administration methods available to clinicians and enable the implementation of long-acting drug depots to reduce patient noncompliance. Further investigation is required before clinical investigation and translation is possible, but this may ultimately prove to be productive in addressing the significant burden of mental health.

Sexual health care

Statistics on Sexual and Reproductive Health (SRH) services in England (2015/2016) revealed that 7% of the resident population of women aged between 13 and 54 years had contacted the SRH services at least once. Furthermore, 19% of women aged between 18 and 19 years had accessed the SRH service at least once.[60] This seems to indicate that effective SRH services might have a significant impact on their health care experience.

Nanomedicine has the potential to offer improvements in reproductive choice and contraceptive safety, and thus provide additional benefit to the well-being of women. For example, copper–curcumin-β-cyclodextrin (Cu–Cur)CD nano-inclusion complexes have demonstrated significant spermicidal effects in vitro. Safety and toxicity results were also favorable, suggesting that this complex could be potentially used as a topical vaginal contraceptive.[61] This type of topical vaginal contraceptive could be implemented as a short-term, nonsteroidal contraceptive measure. However, initial investigations into the potential application of nanomedicine in long-acting reversible birth control are arguably more exciting.

Copper/low-density polyethylene nanocomposite has been shown to have potential for use in intrauterine devices with antifertility effectiveness demonstrated in rats, together with high contraceptive efficacy and fewer clinical side effects compared to other copper intrauterine devices in humans.[62,63] In addition to improving the existing contraceptive measures such as intrauterine devices, nanomedicine may also enable the development of novel longer-acting contraceptive options. For example, a polymeric NP formulation of follicle-stimulating hormone (FSH)-receptor binding inhibitor-8, purified from human ovarian follicular fluid, has demonstrated antifertility activity when studied in vivo in marmosets. In vitro, sustained release of FSH-receptor binding inhibitor-8 was exhibited for 21 days.[64]

Reversible sterilization is an attractive long-term contraceptive option, and early developments have been significantly aided by the use of nanomedicine. Gonadotropin-releasing hormone (GnRH)-conjugated chitosan may represent a promising carrier for the targeted delivery of DNA to GnRH-expressing cells, which could be used to implement noninvasive sterilization by means of gene silencing.[65] Another means of reversible sterilization, smart reversible inhibition of sperm under guidance (Smart RISUG) utilizes nano- to micro-sized magnetic particles in the iron oxide–copper–styrene maleic anhydride–dimethyl sulfoxide contraceptive drug. Drug–sperm interactions are mediated by the presence of a pulsed magnetic field to facilitate better spermicidal action and control of distribution inside either male or female reproductive tubes. Smart RISUG is of significant interest because it is long acting, yet readily reversible.[66] The application of RISUG in men offers the hope of greater shared contraceptive responsibility. RISUG is a promising male contraceptive and has already reached Phase III clinical trial stage.[67–69]

Using nanotechnology to improve and redevelop the existing barrier contraceptives, such as condoms, could have a positive impact on efficacy. For example, graphene and nano-lubricated condoms could offer greater protection for sexual partners.[70] The inactivation of microbial infectiousness by silver NP-coated polyurethane condoms has also been demonstrated.[71]

Although RISUG and nanotechnology-enhanced condoms can provide some level of antimicrobial protection, additional vaccinations, diagnostic tests, and antimicrobial drugs are necessary to prevent and treat sexually transmitted infections.[70–72]

In 2016, women represented 32% of patients receiving care for human immunodeficiency virus (HIV) in England, thus demonstrating the significant impact of HIV on women's health.[73] Although combination antiretroviral therapy has helped to improve the morbidity and mortality of patients infected with this virus, the presence of the virus persists in reservoir organs and treatment remains limited by drug–drug interactions, side effects, and noncompliance.[74] Nanomedicine can aid the provision of such treatment by capitalizing on the ability of nanomedicines to overcome anatomical barriers and to partake in active cell targeting and controlled release.[75] In fact, a Phase I clinical trial has already been underway to compare the relative bioavailability of different

MK-1439 experimental nanoformulations (NFs) with that of a MK-1439 film-coated tablet.[76] In addition, a Phase I clinical trial investigating the pharmacokinetics of the antiretroviral agents efavirenz and lopinavir, administered as NFs in healthy volunteers, is due to begin, pending the acquisition of appropriate funding.[77] Furthermore, nanosuspensions of the non-nucleoside reverse-transcriptase inhibitor TMC278-LA[78] and the intregrase inhibitor GSK1265744[79] are examples of antiretroviral NFs that have been tested in Phase II clinical trials for HIV. Polyethylenimine mannose NPs that carry the HIV antigen-coding DNA plasmid DermaVir Patch vaccine have also reached this phase of development.[80] The potential of vaginally administered agents to target HIV has also been explored. Lecithin/cholesterol-based liposomes that carry MC1220[81] and PLGA NPs which carry rilpivirine are among several NFs to reach the in vivo study stage of development.[82] Proposed methods of nanotechnology-enhanced HIV-1 detection include surface-enhanced Raman spectroscopy using plasmonic NPs; electrochemical detection based on direct electron transfer in the virus; optical detection systems based on localized surface plasmon resonance; and vertically configured electrical detection based on scanning tunneling microscopy.[83]

The proportion of cervical cancers in women which are attributable to human papillomavirus (HPV) infection is in excess of 99%, of which over 75% are attributable to HPV16 and/or 18.[84,85] Phase III clinical trials have shown that the quadrivalent Gardasil vaccine is effective against HPV type 6, 11, 16, and 18 and that the bivalent Cervarix vaccine is effective against HPV type 16 and 18.[86–89] These vaccines consist of virus-like particles that are constructed from L1 capsid monomer protein of the respective HPV types.[90] Biphasic vesicles used for topical delivery of interferon alpha have brought about marked therapeutic effects in patients.[91] The use of biosensors may aid the development of rapid, cost-effective, and accurate diagnostic tests with appropriate sensitivities and detection limits.[92]

The second largest proportional increase in sexually transmitted disease diagnosis in England between 2014 and 2015 was reported for gonorrhea (11%).[93] Nanomedicine may provide a novel means to treat antibiotic-resistant gonorrhea, therefore helping to prevent sequela such as pelvic inflammatory disease. One study showed that nanoencapsulation technology had the potential to enhance adaptive immunity to *Neisseria gonorrhoea* when combined with the intravaginal administration of microencapsulated interleukin-12 (IL-12) in mice. Treated mice responded faster to antibiotics and were significantly less likely to be re-infected than controls, due to the adjunct effects of the IL-12, essentially converting the infection into a live vaccine.[94] A nanobiocomposite platform based on polyaniline-iron oxide-carbon nanotubes (PANI–nFe3O4–CNT) has also been used to fabricate a genosensor for *N. gonorrhoeae* and proven to be effective.[95] A bioelectrode using chitosan–iron oxide nanocomposite also demonstrated a high degree of accuracy for the detection of *N. gonorrhoeae* nucleic acid.[96]

Research has shown that chlamydia detection rates are 1.7–2.2 times higher in women than men, thus reflecting higher testing rates in women.[93] One study demonstrated that when the antibiotic clindamycin hydrochloride, effective against chlamydia, was encapsulated in a poly-lactic acid (PLA)/PLGA-based NP system for oral delivery, enhanced efficacy was noted, as a result of improved bioavailability and drug action.[97] *Chlamydia trachomatis* recombinant major outer membrane protein (MOMP) encapsulated in PLGA NPs has also been shown to trigger primarily T helper 1 (Th1) cells and enhancement of T- and B-cell-mediated immunity in mice and to confer protective immunity against *C. trachomatis*.[98] Furthermore, PLA-poly(ethylene glycol) NPs have been shown to provide sustained delivery of a *C. trachomatis* recombinant MOMP peptide and to potentiate systemic adaptive immune responses in vivo.[99] Encapsulating recombinant MOMP *C. trachomatis* DNA vaccine in biodegradable chitosan NPs facilitates stability and protection from enzymatic digestion, while also enhancing delivery and expression of MOMP DNA in vitro and in mice.[100] Neutral generation-4 polyamidoamine (PAMAM) dendrimer – azithromycin conjugate nanodevices have displayed an ability to deliver drugs efficiently to growing intracellular *C. trachomatis* in vitro.[101] Other studies have demonstrated similarly encouraging findings. Silver-polyvinyl pyrrolidone NPs in mouse macrophages infected in vitro with live *C. trachomatis* exhibit anti-inflammatory effects, possibly due to the regulation of various upstream surface receptors and downstream inflammatory pathway genes.[102] Furthermore, charge-switching synthetic adjuvant particle-based mucosal vaccination elicited protective immune responses in mice.[103] Gold NPs and silver enhancement have been used to enable rapid, simultaneous detection of *Ureaplasma parvum* and *C. trachomatis* antigens by using a method based on visual protein microarray. This may have clinical applications for the simultaneous clinical diagnosis of *U. parvum* and *C. trachomatis*.[104]

The largest proportional increase in sexually transmitted disease diagnosis in England between 2014 and 2015 was reported for syphilis,[93] highlighting the imperative need to

address this issue. A novel quantum dot (QD)-based point of care test for syphilis has been developed.[105] The potential application of Goldmag immune probes, as part of a NP-based colorimetric assay for the detection of syphilis, has also been indicated.[106] In addition, polyelectrolyte-coated gold magnetic NPs have been proven to be sensitive and selective when used in a syphilis immunoassay, suggesting a possible use in point of care diagnostics for syphilis screening.[107]

Consequently, it is already evident that nanomedicine may benefit the health of women by minimizing the side effects of contraceptives. Nanomedicine may also enhance contraceptive efficacy, enabling the refinement of planned pregnancy. Furthermore, it may enable the development of reversible long-term contraceptives suitable for all genders, with the possibility of promoting equality and shared contraceptive responsibility between partners. In addition to contraception, nanomedicine may significantly improve the prevention, diagnosis, and treatment of sexually transmitted diseases which currently pose a significant challenge to women's health. As the diagnosis of bacterial infections increases, it is crucial that an effective arsenal of antibacterial agents is made available to treat such infections and reduce the incidence of serious clinical sequelae. However, with antibacterial resistance making many existing therapeutics redundant, novel treatments may become increasingly important. In addition, viral infections such as HIV and HPV are preventable infections; however, they are also attributable to the development of devastating conditions, namely, acquired immune deficiency syndrome and cervical cancer, respectively. Thus, it is crucial that viral infections are prevented, where possible, with optimized vaccines and barrier contraceptives; diagnosed as early as possible using highly sensitive diagnostic tools and treated before the development of secondary conditions. It is imperative that innovative research into theoretical nanomedicine applications in sexual health is translated into the clinic, to meet the expectations of increasingly scientifically literate patients who deserve the best care with minimal side effects.

Reproductive health care

Research is now underway to allow the field of reproductive science to benefit from the advancements in nanotechnology, by the application of NPs to diagnose and treat common conditions that affect many women of reproductive age, including endometriosis and uterine fibroids.

Endometriosis, which affects 2%–10% of women of reproductive age, involves the development of endometrial-like tissues outside of the uterine cavity[108] and is prevalent in 25%–30% of women suffering from infertility.[109] Conventional imaging of the affected tissues yields limited results, and currently, there is no suitable sensitive serum biomarker for endometriosis. Therefore, development in this field is pressing. NPs may provide the solution for this problem as these engineered particles possess a novel ability to provide excellent contrast enhancements for specific markers. One study demonstrated the production of an enhanced magnetic resonance imaging (MRI) contrast of ectopic uterine tissues in a rat model. The NPs involved were ultra-small superparamagnetic iron oxide NPs (IONPs), achieved through the high affinity of the NPs toward macrophages.[110] Alternatively, magnetic oxide NPs, which had been modified with hyaluronic acid (HA-Fe_3O_4 NPs), have shown potential in detecting lesions.[111] Investigations into the treatment of endometriosis have used the therapeutic gene, pigment epithelium-derived factor (PEDF), which has both antitumor and antiangiogenic properties. Lipid-grafted chitosan micelles were loaded with PEDF and intravenously injected into rats with surgically induced endometriosis.[112] Following treatment, there were significant reductions in ectopic lesion volume. Growth inhibition of endometrioid cysts was also observed. Another study demonstrated that nanoceria (cerium oxide NPs) caused a reduction in the levels of reactive oxygen species (ROS) and angiogenic factors in endometriosis. Regression of endometriosis is also associated with the reduced density of endometrial glands and microvessels.[113]

Uterine fibroids (leiomyomas) are the most common type of pelvic tumor in women of reproductive age, often requiring invasive treatment. NPs have the potential to provide less intrusive treatment options. Cryosurgery offers potential treatment for these tumors. However, reoccurrence is a common drawback. Therefore, one previous study used nanogold particles conjugated with tumor necrosis factor alpha (TNF-α) as a cryo-adjuvant during cryosurgery and demonstrated significant reduction in tumor growth.[114] Another research group investigated an alternative to hysterectomy by using poly L-lysine-PLGA NPs to deliver an antitumor and antiangiogenic biologically active metabolite of estradiol (2-methoxyoestradiol) into a human leiomyoma cell line (huLM).[115] Both of these studies provided evidence of improved activity of the drug compared to the free molecule controls, as typically expected due to NP targeting capabilities. The use of adenovirus as a gene delivery vector to modify diseased cells has also been enhanced by conjugating the virus with magnetic NPs. With the appropriate magnetic field, the group demonstrated a statistically significant suppression of proliferation, and induced apoptosis, in both the cell types.[116]

The emerging evidence described herein suggests promising avenues for the clinical translation of nanomedicine in reproductive health. From imaging to diagnostics and therapeutics, nanomedicine already shows potential to enhance the care available for women of reproductive age with conditions such as endometriosis and uterine fibroids.

Cancer health care

Cancer located in the breasts, uterus, ovaries, and cervix are the first, fourth, sixth, and seventh most common cancers among women in the UK (2015), respectively.[117] There is a growing body of evidence in support for the use of NPs to enable the early and accurate diagnosis of cancer and promote the efficacious treatment of cancers in women. With some new methodologies reaching the clinical trial phase of development, in time, nanomedicine may provide significant, state-of-the-art treatment options for women, subject to further investigation.

Currently, the imaging of cancer tissues by methods such as MRI, computed tomography (CT), and positron emission tomography is restricted by the use of nonspecific contrast agents, which only provide limited morphological information. The properties of NPs, such as paramagnetic particles, can be applied to provide a tissue-specific contrast for imaging and therefore provide a much more detailed image for diagnostic purposes.[118]

The principle of conjugating ligands targeting cancer-specific receptors with paramagnetic NPs is available for some time. For example, in ~20%–30% of breast cancers, the tyrosine kinase human epidermal growth factor receptor 2 (HER2)/neu receptor is overexpressed.[119] In 2003, a study demonstrated how IONPs conjugated with molecules that targeted this receptor could be manipulated to improve MRI contrasts.[120] A more recent study showed how NPs coated in biocompatible material could be used to increase lifespan in the circulation. In this study, iron paramagnetic NPs were coated with HER2/neu antibody-conjugated poly(amino acid) derivatives (PAION-Ab)[121] and showed specific targeting to SKBR-3 cells, which overexpressed the receptor and thus possess the potential to be a good MR contrast agent. This principle, however, is yet to be tested in vivo. Another study demonstrated promising in vivo results for targeting HER2- or epidermal growth factor receptor (EGFR)-positive breast cancer cells, by using conjugated IONPs with a block copolymer PEO-*b*-PγMPS to reduce the nonspecific uptake of the NPs by macrophages.[122] This increases the availability of the circulating NPs to the cancer cells and therefore has the potential to increase tissue-specific uptake and subsequently signal intensity under MRI.

Regarding ovarian cancer, current imaging methods are incapable of detecting tumors <0.5 cm;[123] this must be improved for both detection and treatment purposes. It has been reported that 90% of solid ovarian cancer tumors overexpress the folate receptor alpha; therefore, NPs targeting this receptor offer potential benefits.[123,124] Folic acid (FA)-targeted IONPs have been developed as a T2-negative contrast agent for MRI. It has been demonstrated in a xenograft tumor mouse model that FA-targeted IONPs specifically targeted the Skov-3 cells (with overexpressed FA receptors). Therefore, there is a potential to specifically localize carcinoma tissues, using the NPs as a negative contrast.[125] Another group used polyethylenimine-entrapped gold NPs, which were modified with a FA-linked polyethylene glycol (PEG) to form (FA-Au PENPs), to be used as a nanoprobe for CT imaging of cells which overexpressed the FA receptor.[126]

MRI/CT imaging can leave much to be desired in terms of the resolution of tumor images, especially with tumors of small diameter. Therefore, one group by using a combination of photo acoustic tomography which has good resolution and imaging depth and fluorescence molecular tomography which provides 3D optical imaging used an NP contrast to provide images of ovarian cancers.[127] HER2/neu-specific affibody conjugation to imaging and quantification of IONPs was labeled at the cysteine residue of the affibody with near-infrared dye (NIR-830 dye). This proposed method provides a more advanced imaging prospect, specifically for ovarian cancer, and thus has promising clinical implications.

Cervical cancer screening is an important aspect of women's care, identifying women at risk of developing or who have developed cervical cancer. Initially, QDs conjugated to anti-EGFR antibodies were studied for the replacement of the organic dyes used in histological analyses.[128] However, it was found that ultra-bright fluorescent mesoporous silica NPs, functionalized with FA, exhibit greater fluorescence and have thus been developed to distinguish precancerous and cancerous cervical epithelial cells.[129] These NPs significantly increased the sensitivity of testing compared with currently available tests such as HPV-DNA and pathology tests.

A metastasizing cancer will often release cancer cells into the blood stream, and it could therefore be possible to detect these cells in a blood sample. However, the concentration of cancer cells can be very small and therefore difficult to identify. Serum detection for ovarian cancer is limited, but NPs may offer new techniques. One research group has developed a technique to separate and detect ovarian cancer cells from female whole blood using FA-conjugated

magnetic IONPs.[130] Unlike the previously discussed FA imaging methods, these NPs aim to mechanically separate cancer cells from other blood cells and are able to bind with metastasized cells overexpressing the FA receptor in a sample of whole blood. The sample is placed on a magnetic separator, and the pellet containing the IO–FA NP captured cells can be examined. This provides a method of identifying minute quantities of circulating ovarian cancer cells and could thus provide a means of early detection to enhance treatment options.

The detection of circulating breast cancer cells has been explored using a nanostructure-based platform for rare cell capture; this technique relies upon the platform's increased surface area. The streptavidin-conjugated silicon nanowire was shown to identify 16.2±5.5 cells per 0.5 mL of whole blood.[131] Dual aptamer-modified silica NPs have also been developed which target two cell lines, mucin 1 and human epidermal growth factor receptor 2 (EGRF2). This system will allow for the identification of two different types of breast cancer cells, thus enabling a broader range of diagnosis. Moreover bespoke NPs (dye-doped), in which dye molecules are directly incorporated in the NPs, lead to the creation of highly fluorescent NPs. This technique boasts a 1 cell/100 µL detection limit, which is much better than that reported in previous studies.[132]

Sentinel lymph nodes are the lymph nodes in which cancer tissues drain. Thus, if a cancer has metastasized, there will often be cancer cell parents in these lymph nodes. While operating to remove breast tumors, surgeons must identify the sentinel lymph nodes to allow for a biopsy of these lymph nodes to be taken as these can be histologically analyzed to confirm whether the cancer has metastasized. Current techniques include radiocolloid tracer, isosulfan blue dye, and indocyanine green (ICG).[133] These either require specialist gamma tracing equipment or, in the case of isosulfan blue dye, cause anaphylactic shock in 1.1% of patients.[134] Carbon NPs have been proposed to replace these techniques as the black appearance of the NPs can be detected by the operating surgeon to identify the correct lymph nodes to biopsy. Injection of 1 mL of carbon NP suspension leads to a significantly increased identification rate and also reduced false negative compared with blue dye (carbon NP versus blue dye: identification rate 100% versus 88%, false negative 11.1% versus 15.8%).[135] Due to their 150 nm diameter, carbon NPs are unable to enter the circulation, thus providing a distinct advantage (Figures 2 and 3).

Progression in the field of NPs has recently shifted toward sugar-based NPs. Some cancer cells are preprogramed to internalize sugar-based molecules at a faster rate than normal cells as some have an increased expression of glucose transporters (GLUT), described by the Warburg effect.[136] The fluorescent dye, ICG, was combined with NPs by encapsulation in levan NPs via self-assembly to demonstrate the effectiveness of sugar-based NPs. Without encapsulation, ICG has a very short half-life in the human environment, and so encapsulation helps to stabilize the dye, and the activity is preserved. These NPs were shown to successfully accumulate in breast cancer cells due to the increased expression of GLUT. Levan, in particular, has fructose moieties that interact with GLUT5 and pose new avenues for the exploration of drug delivery and imaging.[136]

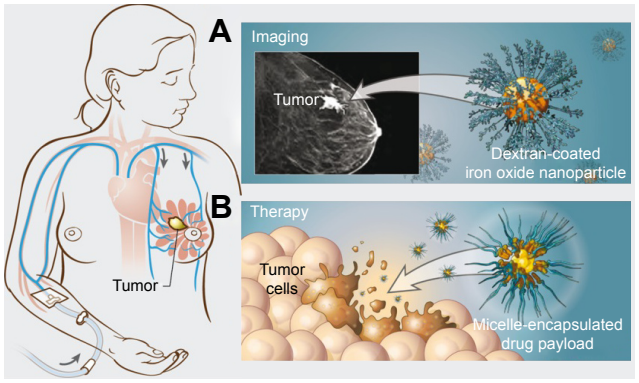

Figure 2 Nanoparticles in cancer management.
Notes: Nanoparticle accumulation at the tumor site can be used to deliver (**A**) contrast agents such as dextran-coated iron oxide nanoparticles for magnetic resonance imaging (MRI) or (**B**) chemotherapeutic drugs encapsulated in nanomaterials such as micelles. Reproduced with permission of Annual Review of, Volume 14 © by Annual Reviews, http://www.annualreviews.org. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. In: Yarmush ML, editor. Palo Alto, CA: *Annual Review of Biomedical Engineering*. Vol 14. 2012:1–16.[3]

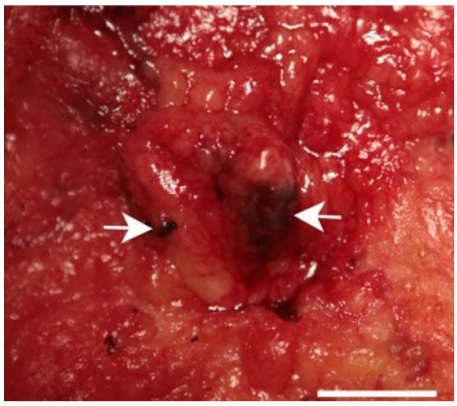

Figure 3 A photograph demonstrating the black-dyed lymph nodes (shown by the white arrows) in breast tissue 1 day postinjection of nanoparticle carbon suspension.
Notes: Scale bar is 1 cm. Reprinted from *Diagn Microbiol Infect Dis*, 67(2), Tang JF, Xu ZH, Zhou L, Qin H, Wang YF, Wang HH, Rapid and simultaneous detection of Ureaplasma parvum and Chlamydia trachomatis antibodies based on visual protein microarray using gold nanoparticles and silver enhancement, 122–128, Copyright (2010), with permission from Elsevier.[104]

Treatment of cancer is complex due to the incredibly varied properties of different cancers. Therefore, NPs have been developed to target cancers in a variety of ways. First, some NPs have been developed to sensitize the cancerous tissues to currently available drugs. For example, in ovarian cancer, the functionalization of nanoscale gold particles with thio-glucose-targeting ligands has been shown to facilitate the delivery of chemotherapeutic agents into ovarian cancer cells. In addition, NPs also exhibited radio-sensitizing effects upon a human ovarian cancer cell line (SK-OV-3), believed to result from the increased production of ROS.[137]

Enhancing drug delivery can also be facilitated by NPs. This is of particular interest as cancer drugs are often very cytotoxic to other noncancerous tissues. Choriocarcinoma is a malignant, trophoblastic cancer of placental origin, which is typically located in the uterus but may also occur in extrauterine sites such as ovaries. EnGeneIC delivery vehicles (EDVs) have shown potential for use in the targeted NP delivery of doxorubicin into placental tissues with greater antitumor activity in mouse models of choriocarcinoma relative to the free drug. Therefore, these high-capacity nanospheres, which may be targeted to EGRF to reduce non-trophoblastic drug delivery, may prove to be a promising drug delivery system for the treatment of choriocarcinoma.[138] A phase 1 clinical trial (ACTRN12609000672257) in nonpregnant human subjects with advanced epithelial cancer has shown that EDVs are safe in patients with advanced solid tumors and display modest clinical efficacy.[139] Neoadjuvant NP-albumin-bound paclitaxel (nab-PTX) is a treatment currently used for certain cancers due to the associated albumin receptor and SPARC affinities to albumin. This has also been suggested as a feasible therapeutic option for recurrent cervical cancer, being tolerable and potentially effective even after patients fail to respond to platinum-taxane or topotecan chemotherapy.[140] A meta-analysis investigated nab-PTX compared with PTX for breast cancer treatment and concluded that in randomized trials, there was a significantly greater chance of achieving a pathological complete response, an indication of better long-term outcome. This review also found that nab-PTX reduced the number of hypersensitivity reactions, one cause of these being the solvents used to make PTX into a soluble form, which is not necessary with nab-PTX. This provides solid evidence to support the use of nab-PTX.[141] Ovarian cancer-targeted PTX NPs, which had been modified with FSH beta 81-95 peptide, were shown to successfully deliver chemotherapeutic compounds into ovarian cancer cells.[142] Similarly, folate (FOL)-mediated PLGA-PEG NPs containing PTX, a drug that interferes with normal microtubule function, were delivered to endometrial carcinoma HEC-1A cells. Results highlighted an enhanced level of tumor targeting and efficiency, which was significantly better than with the free drug alone.[143]

Combination drug therapies have also been manipulated by NPs. Transactivation of transcription-targeted solid lipid NPs are a promising drug delivery system. This may enable the co-delivery of PTX and tocopheryl succinate-cisplatin as a combination therapy, which shows effective and synergistic antitumor activity against cervical cancer.[144] In breast cancer, neuropeptide Y Y1 receptors are overexpressed in comparison with normal breast cells which only express neuropeptide Y Y2. Capitalizing on these properties, one research group developed a conjugate molecule of doxorubicin and PNBL-NPY, the Y1 receptor ligand. This was internalized by the MCF-7 breast cancer cells which caused significant inhibition of cell growth, due to the drug, but also due to the synergistic interactions at the neuropeptide receptor.[145]

Cancer cells can develop acquired drug resistance, and in general, drug-resistant cells prevent intracellular drug accumulation. Therefore, NPs are being modified to bypass these cellular defence systems.[146] Several types of NPs have been developed to target cervical cancer. NP delivery of siRNA against TWIST (a transcription factor reactivated in cancer) was used to reduce cisplatin resistance and resulted in reduced tumor burden in mice treated with cisplatin plus MSN-siTWIST, compared with mice treated with cisplatin alone. This was due to the reduction of disseminated tumors.[147] Another method to bypass cisplatin resistance is F3-targeted cisplatin-hydrogel NPs. This has been shown to be an effective therapeutic which can overcome the resistance of human ovarian tumor endothelial vessels to chemotherapy in vivo.[148] PTX can also be loaded into cationic nanostructured lipid NPs and has the potential to overcome PTX resistance and display therapeutic efficacy both in vitro and in vivo.[149]

Another mechanism for cancer treatment is the enhancement of apoptosis in cancer tissues by stimulating specific mechanisms and causing a reduction in tumor mass. This has been well studied in cervical cancer. For example, folate receptor α (FRα)-targeted nanoliposomes inhibit proliferation and induce apoptosis of cervical tumor cells in vivo, while exhibiting no significant toxicity, suggesting that this may represent a novel modality for gene therapy in the treatment of cervical cancer.[150] Nanoquinacrine has also been shown to induce apoptosis in cancers through the inhibition of HH-GLI cascade by GLI1-inducing apoptosis of cervical cancer stem cells.[151] Also, nanorealgar can inhibit the proliferation of different cervical carcinoma cell lines and

induce apoptosis in cervical carcinoma cells.[152] In ovarian cancer, the combination of salinomycin and silver NPs has been shown to increase the therapeutic potential of the chemotherapy agent by enhancing apoptosis and autophagy in human ovarian cancer cells.[153] Furthermore, the induction of apoptosis and inhibition of angiogenesis by PEGylated liposomal quercetin showed significant suppression of tumor growth, compared with free quercetin, in in vitro and in vivo models of cisplatin-resistant ovarian cancers.[154] In SKBR-3 (HER2 positive cells) breast cancer cells, the induction of cell death was stimulated by the delivery of YopJ, an effector from the bacteria *Yersinia pestis*, fusing with glutathione S-transferase to form self-assembled protein NPs. This was found to downregulate MAPK and NFκB pathways, induce cell death, and inhibit the MEK1 pathway, and thus has the potential for reversing some drug resistance.[155]

Gene therapy is a pioneering area of cancer medicine. The ability to transfer a gene with the intent to cause a change in cellular mechanisms is highly promising. Encapsulating molecules such as siRNA can protect such material from RNase degradation in circulation. For example, T7-LPC/siRNA NPs were shown to deliver EGFR siRNA into breast cancer cells through receptor-mediated endocytosis and then induce the downregulation of EGFR. This inhibited the growth of tumour.[156] Another example is that chitosan/HPV16 E7 siRNA complexes in cervical cancer cells were shown to target two oncoproteins and induce apoptosis, thus suggesting these might represent a useful NP system for the treatment of cervical cancer.[157] In addition, TNF-related apoptosis-inducing ligand/endostatin-loaded NPs have also been suggested as cervical cancer gene therapy modalities, on account of their enhanced cytotoxicity.[158] In ovarian cancer, antitumor effects were observed in studies where PLGA NPs encapsulating the proapoptotic human PNAS-4 (*hPNAS-4*) gene, along with cisplatin, were delivered into mouse ovarian carcinoma cells.[159] Degradable NPs have been used to deliver the proapoptotic survivin *T34A* gene and were shown to inhibit tumor growth in a mouse xenograft model of SKOV3 human ovarian cancer.[160] In addition, it has been found that Fe_3O_4-dextran-anti-βHCG carrying Hpa-antisense oligodeoxynucleotide has the potential to be an effective gene therapy for choriocarcinoma with significant inhibitory effects displayed on transplanted choriocarcinoma tumors in vivo. In this way, NPs can function as a harmless and effective gene vector.[161,162]

Thus far, the most significant medical research and clinical translation in the field of nanomedicine has been related to the subject of oncology. Specific visualization and quantification of pathological processes, combined with the delivery of multiple simultaneous targeted payloads of chemotherapeutics, NP-delivered gene therapy, and reduced incidence of drug resistance all offer significant hope of improving the prognosis of women receiving treatment for their respective cancer(s).

Menopause-related health care

Menopause occurs when the ovaries cease to make estrogen. Menopause is marked by the ending of a woman's menstrual cycles and may be initiated by the surgical removal of the ovaries. Menopausal symptoms are typically experienced, and the long-term reduced levels of estrogen can result in health problems, such as osteoporosis and cardiovascular disease.

Hormone therapy is the best available treatment for the vasomotor symptoms of menopause[163] and has the additional benefit of promoting an increase in bone density, thereby reducing the risk of fracture among postmenopausal women.[164] However, clinical trial results[165,166] revealed that both estrogen alone and estrogen with progestin significantly increased the risk of stroke. Estrogen and a progestin were also associated with a significantly increased risk of breast cancer, coronary events, and pulmonary embolism. Consequently, the use of hormone therapy has declined.[167] However, micellar NP estradiol emulsions offer hope for enhanced transdermal hormone replacement therapy, which retains the advantages of transdermal administration while reducing adverse local side effects. Potential advantages of this technique include a lower incidence of venous thromboembolism and stroke and avoidance of first-pass metabolism when compared to oral administration.[168,169] This represents the first product of its kind with the capacity to deliver consistent, therapeutic levels of estradiol systemically and to reduce the vasomotor symptoms observed in postmenopausal women.[170] Additional benefits include improved safety and greater patient compliance than other transdermal delivery systems.[171] The findings of a Phase II clinical trial showed that treatment with nanoparticulate transdermal hormone therapy (nanoparticulate estradiol and nanoparticulate progesterone) for 12 weeks had beneficial, or neutral, effects on anthropometric markers of inflammation and hormonal variables in postmenopausal women, with no clinical evidence of cardiovascular disease. Of particular interest was the observed reduction in C-reactive protein and fasting insulin levels; known markers for chronic inflammation and cardiovascular risk, respectively.[172,173]

Osteoporosis is a major health concern which arises due to long-term estrogen reduction at menopause. However, the application of nanomedicine offers the hope of improved

diagnostics and therapeutics, bone tissue engineering, nanostructure implantable materials, and surface modifications and coatings, which may provide a means of managing postmenopausal osteoporosis. Nanostructured ceramics, polymers, metals, and composites, which enhance osteoblast function and which have greater surface area and roughness to promote osteointegration, are of significant interest. The use of antimicrobial and drug-eluting coatings may help to improve the safety of surgical interventions by preventing infection.[174] The possibility of rebalancing bone turnover, using nanomedicine as a means of stabilizing osteoporosis, is of great interest. For example, calcium phosphate (including hydroxyapatite and β-tricalcium phosphate) NPs exhibit excellent biocompatibility, biodegradability, and biological activity, and therefore seem to be suitable vehicles for bone-specific drug delivery.[175] Furthermore, risedronate/zinc-hydroxyapatite NPs have been shown to represent a positive countermeasure to treat rat-modeled postmenopausal osteoporosis by means of rebalancing bone turnover in favor of bone formation.[176] Another study proposed the use of bisphosphonate (Bis)-conjugated iron (II, III) oxide (Fe_3O_4) NPs as a novel treatment for osteoporosis. These authors used a water-dispersible magnetic NP, which had radiofrequency-induced thermogenic properties to reduce the activity of osteoclasts through thermolysis.[177] Alternatively, the orally available enteric-microencapsulated parathyroid hormone (1-34)-deoxycholic acid nanocomplex may have the potential to effectively treat osteoporosis based on observations showing improvements in osteogenesis and trabecular connectivity in the ovariectomized rat model.[178] These studies reveal that there may be significant improvements to be made in reducing the development of postmenopausal osteoporosis through the administration of targeted nanotherapeutics.

Experimental evidence suggests that NPs may have the capacity to enhance the diagnostic imaging and treatment of postmenopausal cardiovascular disease.[179] Suppression of in-stent neointimal growth was observed in rabbits treated with liposomes carrying prednisolone phosphate[180] while liposomes carrying dexamethasone resulted in anti-inflammatory effects in atherogenic mice.[181] Furthermore, anionic micelles and NP-apoB100 antibody conjugates have successfully reduced low-density lipoprotein levels in vivo.[182] Another study showed that fullerenes carrying vimentin displayed antioxidant and anti-inflammatory effects within cells in an adipose tissue model.[183] Experimentally, perfluorocarbon NPs carrying fumagillin and theranostic NPs carrying 5-(4-carboxyphenyl)-10,15,20-triphenyl-2,3-dihydroxychlorin have been successfully applied to MRI imaging, targeting [alpha]v[beta]3 integrin and macrophages respectively.[184,185]

Menopause can result in the development of significant and potentially life-threatening sequelae such as osteoporosis and cardiovascular disease. Women are almost inevitably subject to the effects of menopause, which makes it an important area for the advancement of health care provision. Nanomedicine may reveal sophisticated approaches to improve the management of menopausal symptoms and the imaging, diagnosis, and treatment of sequelae.

Early-onset dementia health care

Data published by Alzheimer's Research UK suggests that dementia is the leading cause of death among women in the UK. It is estimated that women constitute 61% of people living with dementia, while 39% are men. This proportional difference is likely to result from the fact that age is the largest risk factor for this condition, and women typically live longer than men.[186] However, other factors should be considered. It is necessary to identify gender-specific risk factors in order to substantiate the hypothesis that women are more likely than men to develop dementia at any given age. Currently, there is a lack of firm evidence to support this view, but evaluation of the relative ratio of early onset dementia diagnoses in men and women may help to test this hypothesis.

Although Alzheimer's disease (AD) and other forms of dementia are primarily considered to be degenerative diseases of old age, ~4% of people with AD are under the age of 65 years.[187] This section of the review presents a synopsis of the applications of nanomedicine in the diagnosis and treatment of AD, which in rare circumstances can affect cisgender women between puberty and menopause.

Studies investigating the applications of nanotechnologies in the diagnosis of AD have yielded promising results, suggesting that improvements in both the early imaging of AD-affected brains and the detection of AD biomarkers may be possible.[188] The detection and identification of amyloid plaques by MRI, using NPs doped with contrast agents or tagged with fluorescent probes, is of particular interest. IO and gold NPs, thioflavin T, and QDs have all been explored in this context.

The successful detection of amyloid in transgenic mice using monocrystalline IONPs, covalently tethered to the N terminus of amyloid beta ($A\beta$) peptide for MRI, has already been reported.[189] Furthermore, the synthesis of fluorescent-maghemite NPs has created a method to use multimodal imaging agents to detect and remove amyloid fibrils by

manipulation with an external magnetic field.[190] In addition, the synthesis of superparamagnetic IONPs, coated with a 1,1-dicyano-2-[6-(dimethylamino)naphthalene-2-yl]propene carboxyl derivative, has been investigated in vitro for MRI studies of AD. Fluorophotometry results showed that the combination contrast agent resulted in the enhancement of fluorescence.[191] The potential of metal NPs is further evident with the example of gold NPs. Noninvasive, label-free nanoplasmonic optical imaging for the real-time monitoring of amyloid fibrogenesis in vitro has been developed, observing the random movements of gold NPs in Aβ solution, and quantifying the kinetics of the fibrogenesis. It is hoped that this technology may eventually enable long-term monitoring of neuronal cells to aid in the identification of the mechanism of amyloid growth.[192] Furthermore, heterodimeric NPs, consisting of a cobalt (II) magnetic core and a platinum shell fused to gold NPs and stabilized by a lipoic acid–PEG coating, have been used successfully in conjunction with MRI to image Aβ protofibrils in the early reversible stages of Aβ self-assembly.[193]

Further innovative imaging methods are under development. One study showed that thioflavins, released from NPs administered via intracerebral injection, have the potential to target fibrillar amyloid in vitro and in vivo in the hippocampus of transgenic mice.[194] Therefore, thioflavin-loaded NPs represent another possible methodology in need of translational experimentation. In addition, novel QD nanoprobes have also been shown to be effective in the real-time imaging and quantification of Aβ peptide aggregates in vivo.[195] Moreover, a QD probe, conjugated with Aβ antibody for the molecular imaging of AD in a mouse model, confirmed the possibility of tracking the state of Aβ in vivo accumulation in mice, indicating a potential use in the molecular diagnostic imaging of AD in humans.[196]

In addition to imaging, detection of biomarkers for AD (Aβ peptide and tau) is a key area of investigation in nanomedicine. The development of biosensors has been significantly aided by the advent of nanomedicine, with several developments having the potential to improve the diagnosis of AD. Indeed, the development of NP-based bio-barcodes, involving oligonucleotide-modified gold NPs and magnetic microparticles, has permitted the detection of soluble pathogenic biomarkers for AD in cerebral spinal fluid.[197] Furthermore, the electrochemical detection of Aβ by saccharide-immobilized gold NPs on a carbon electrode demonstrated low detection thresholds, making this a promising methodology that requires further investigation.[198] In addition, scanning tunneling microscopy has been applied to the electrical detection of AD biomarkers with the production of a similarly ultrasensitive immunosensor for Aβ, capable of detecting concentrations exceeding 10 fg/mL.[199] The development of gold NP-based immuno-polymerase chain reaction (nano-iPCR) further enabled the detection and quantification of tau protein in cerebrospinal fluid. Data indicated that Nano-iPCR is superior than ELISA in terms of sensitivity and detection range for tau protein detection, revealing the possibility of substantial improvements in the detection of biomarkers for AD.[200] An alternative exploitation of the properties of gold NPs saw the development of an ultrasensitive and highly selective method of detection suitable for AD biomarker tau protein. Utilizing the two-photon Rayleigh scattering properties of gold NPs, anti-tau antibody-coated gold NPs proved to be highly sensitive to tau protein and suitable for further translational investigation.[201]

Research has already begun into the potential use of nanotechnology applications of nanoscale inhibitors of Aβ plaque formation, nanoscale antioxidants, and NP-delivered cholinesterase inhibitors to treat AD.[202] It could be argued that, to date, the most successful method of minimizing cognitive defects through the nanoscale inhibition of Aβ plaque formation has been the implementation of hydrophobic chelating agents. The hydrophobicity of these agents aids their passage across the blood–brain barrier, while their ability to sequester metal ions, which can accelerate the formation of Aβ plaques, reduces plaque development. Such agents have progressed to pilot Phase II clinical trials with metal-protein attenuation demonstrated by iodochlorhydroxyquin showing modest efficacy in AD patients.[203] In addition, NPs carrying novel D-penicillamine have also been proposed for metal chelation therapy in AD as a result of their observed ability to dissolve pre-existing Aβ aggregates in vitro.[204] Although most investigation into the use of nanoscale inhibitors of Aβ plaque formation remains at the preclinical stage of development, there are several promising lines of investigation. For example, resveratrol has been shown to reduce the accumulation and deposition of Aβ in vivo by controlling AMPK signaling. In this way, the neuroprotective action of the kinase against Aβ plaque accumulation and deposition may suggest appropriate lines of investigation for the development of novel treatments for AD.[205] In addition, PEGylated phospholipid nanomicelles have been shown to interact with Aβ in vitro, thus mitigating Aβ plaque formation, aggregation, and neurotoxicity in the SHSY-5Y human neuroblastoma cell line.[206] KLVFF beta sheet blocker peptide-loaded liposomes have also been said to represent a

potential treatment to prevent amyloid aggregation in AD, because of their good colloidal stability and surface tension–lowering abilities.[207] An alternative means of diminishing the aggregation and neurotoxicity of amyloid is by using pullulan-modified cholesteryl nanogels which bind to Aβ oligomers, thus acting as chaperones for misfolded proteins in primary cortical neuron cultures in vitro.[208]

As outlined earlier, nanomedical innovation is promoting the investigation of curcumin as an alternative therapeutic across a wide range of medical applications. Indeed, curcumin-associated nanoliposomes are known to inhibit the aggregation of Alzheimer's Aβ peptide in vitro.[209] Similarly, nanoliposomes carrying a curcumin-lipid derivative, and decorated with an anti-transferrin monoclonal antibody conferring brain targeting functionality, have proven to be successful in delaying Aβ peptide aggregation, thus indicating a potential role in the treatment of AD.[210]

C60 fullerene is a well-characterized free-radical scavenger and in its hydrated form has demonstrated the ability to inhibit fibrillization of Aβ peptide. In addition, the intraventricular administration of hydrated C60 has been shown to reduce Aβ-induced cognitive impairments in rats. C60 fullerenes therefore exhibit multiple synergistic mechanisms which could potentially be exploited in the treatment of AD, warranting further translational investigation of fullerenes as neuroprotectants.[211]

Increasing cholinergic activity, through the delivery of cholinesterase inhibitors using nanoscale drug delivery systems, is another therapeutic route being explored. Rivastigmine, a hydrophilic cholinesterase inhibitor, delivered in liposomes, offered a profound therapeutic effect that was greater than when delivered as a solution in an aluminum chloride (AlCl(3))-induced Alzheimer's rat model. The liposomes offered greater improvement than the solution in terms of spatial memory; histopathological examination of rat brains also showed substantially reduced amyloid plaque formation.[212] Furthermore, nanodelivery systems may also enable the therapeutic use of acetylcholine. For example, the administration of acetylcholine alone in a kainic-acid-induced mouse model of AD did not bring about any significant effect, probably due to its poor ability to cross the blood–brain barrier and its short half-life.[213] However, single-walled nanotubes loaded with acetylcholine restored cognitive function to pre-AD levels. If administered within a lysosome-specific, cytotoxicity-free dose range, it is possible that translational research may enable the implementation of therapeutic acetylcholine alongside cholinesterase inhibitors to increase cholinergic activity.

The development of effective treatments for AD has been hindered by the uncertain mechanisms underlying progression of the disease and limited investigational capacity in humans, on account of the complexity and relative isolation of the brain, which frequently demands invasive procedures. The existence of just two main biomarkers for AD makes diagnosis of the disease challenging. Such challenges may potentially interfere with the results of clinical trials, and incorrectly diagnosed patients could even be recruited by such trials. Although the health care and clinical outcomes of AD patients currently lag behind that of many other diseases such as cancer, nanomedicineve has the potential to support developments in this field. These developments might include improved imaging, which could enable research to offer a better understanding of the disease processes, more sensitive diagnostic tools to improve the early and accurate diagnoses of the disease or provide more effective treatments by exploiting the properties of nanomedicine to enhance the efficacy of the existing and novel therapies. Nanomedicine can thus assist in bringing about landmark developments necessary to improve the well-being of AD patients. That being said, much investigative works are still to be done to devise methodologies appropriate for translation into humans.

Conclusion

The clear advancements being made in the field of NPs can, in part, be attributed to their highly favorable characteristics. A vital property of NPs is their ability to target a specific ligand/receptor of a cell (Figure 4). This adaptable feature of NPs allows researchers to manipulate the natural biology of diseased cells, creating NPs containing pharmaceuticals which can then target the specific diseased cells. Coupled with the enhanced surface area of NPs, this also leads to a greater ability to detect small numbers of cells, with specific target ligands/receptors in samples, and thus provides an excellent way of detecting disease. Furthermore, loading NPs with pharmaceuticals has been shown to improve the bioavailability of drugs, for example, by protecting the drugs from the internal environment, and therefore improving pharmacological performance. Loading can also lead to the sustained release of pharmaceuticals, as NPs can act as local deposits for drugs. This could thereby reduce noncompliance problems associated with drug efficacy.

Although significant progress is being made, there are still many potential pitfalls in the translation of nanomedicine into clinical practice. One of the most important issues is the potential toxicity of the particles themselves. These foreign, and synthetic, molecules are known to exhibit a

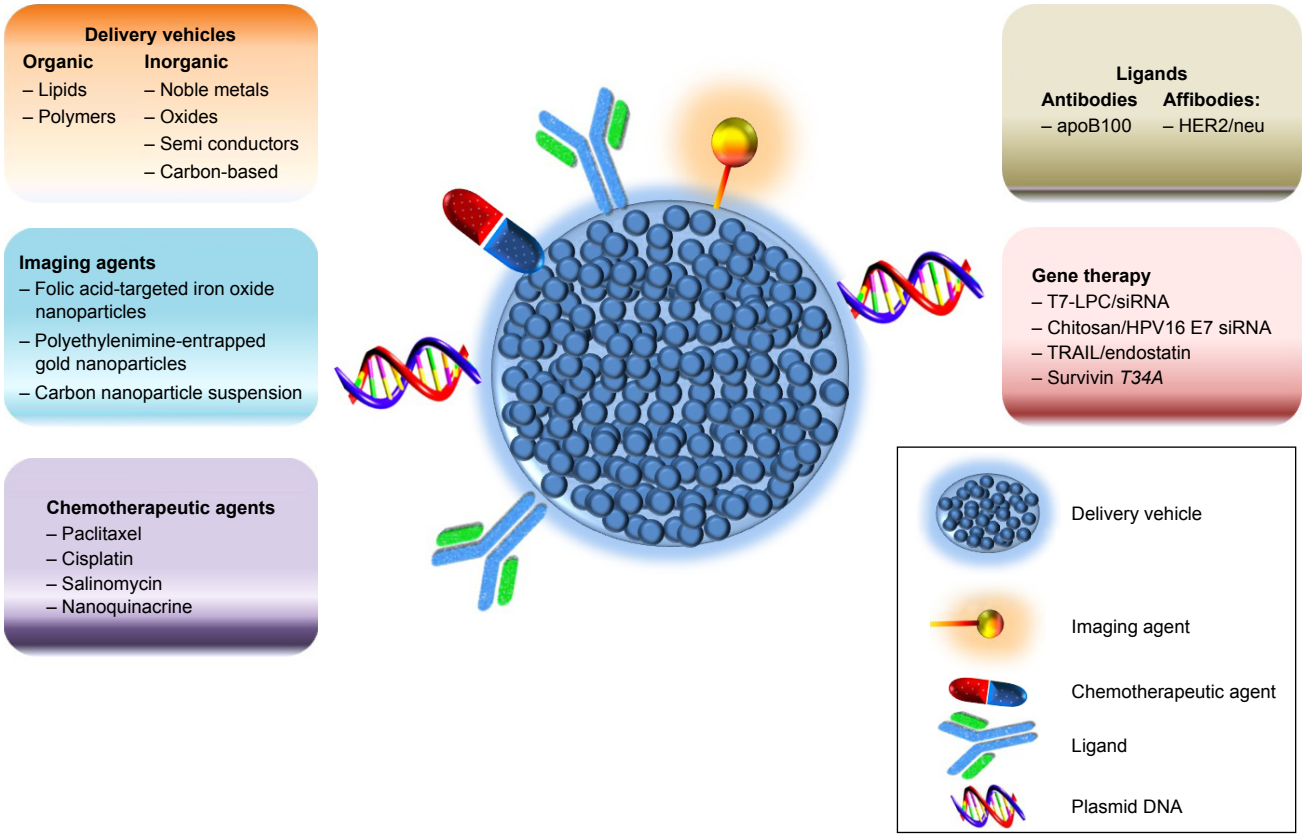

Figure 4 Clinical applications of nanoparticle-based delivery system in women's health. Nanoparticles have been used in drug delivery, imaging, and gene therapy.
Abbreviations: TRAIL, TNF-related apoptosis-inducing ligand; TNF, tumor necrosis factor.

variable degree of cytotoxic effects upon human cells. Further research must now concentrate on this potential barrier, focusing particularly on the composition of the NPs and the ligands present on their exterior, together with the metabolic fate of such particles. Particular emphasis should be directed toward finding techniques to form NPs at a low cost with as little specialist equipment as necessary. This would make such treatment more accessible in the future.

The life course of a woman presents a unique set of medical challenges that are yet to be adequately addressed by the medical field. It is hoped that nanomedicine can provide promising and novel therapeutic applications, to allow physicians and patients to address these challenges more effectively. This review was intended to present a synopsis of the contribution nanomedicine could offer to the treatment of women's health and to encourage researchers to assist in the translation of this exciting technology to the clinic. Ample justification for such future effort is clearly evident in the primary literature, which already shows an abundance of primary research papers offering exciting and efficacious applications for nanomedicine in the treatment of women's health.

Disclosure

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