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Nanotechnology in reproductive medicine: Emerging applications of nanomaterials

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Abstract

In the last decade, nanotechnology has been extensively introduced for biomedical applications, including bio-detection, drug delivery and diagnostic imaging, particularly in the field of cancer diagnostics and treatment. However, there is a growing trend towards the expansion of nanobiotechnological tools in a number of non-cancer applications. In this review, we discuss the emerging uses of nanotechnology in reproductive medicine and reproductive biology. For the first time, we summarise the available evidence regarding the use of nanomaterials as experimental tools for the detection and treatment of malignant and benign reproductive conditions. We also present an overview of potential applications for nanomaterials in reproductive biology, discuss the benefits and concerns associated with their use in a highly delicate system of reproductive tissues and gametes, and address the feasibility of this innovative and potentially controversial approach in the clinical setting and for investigative research into the mechanisms underlying reproductive diseases.

Key words: Nanomaterials; Reproductive medicine; Reproductive biology; Infertility; Gametogenesis

Nanotechnology is an integrative discipline, which represents a unique combination of classical natural, mathematical, computer and materials sciences, investigating and manipulating physical matter on the scale of nanometers.[1] The unparalleled potential of engineered sub-micron structures, which are comparable in size to biological molecules, has been recognized ever since the 1950s.[2] However, the rapid development of applied nanotechnology only began in the 1990s following the discovery of the Nobel Prize-winning technique, scanning tunnelling microscopy,[3] and, several years later, atomic force microscopy.[4] Both these methods, which allow the visualisation and handling of small-scale physical matter with exceptional accuracy, triggered an exponential growth in nanoscience.

By the year 2000, nanotechnology was universally recognised as a landmark innovation, and named "the sixth truly revolutionary technology introduced in the modern world".[5] In response to the widespread practical applications of nanotechnology, many countries have introduced specialised courses in nanoscience as part of high-school, undergraduate and graduate curricula, and promoted dedicated international research initiatives.[6,7]

Over the last decade, nanotechnology has been extensively introduced into biomedical applications, including biological detection, drug delivery, diagnostic imaging, and tissue engineering.[1,8] This action resulted in dramatic improvement in the diagnostic and therapeutic values of these methodologies.[9] Estimates suggest that the number of nanotechnology patents related to healthcare has increased from less than 200 in the year 2000 to nearly 10,000 by the year 2010, doubling almost every three years, and thus reflecting the rapid expansion of this pioneering industry.[10]

Traditionally, the main scope of fundamental and applied nanobiotechnology lay in the field of cancer diagnostics and treatment, inseparable from the challenge of selecting and destroying affected cell populations with ultimate precision.[11] However, on-going improvement in the safety of biomedical nanomaterials, along with the accumulation of experimental

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Table 1
Common biomedically-applied nanomaterials.

Class	Subclass	Material	Structure	Description
Organic	Lipids	Phospholipids	Liposomes	Enclosed nanospheres comprised of a phospholipid bilayer
			Micelles	Enclosed nanospheres comprised of a phospholipid monolayer
		Solid lipids	Solid lipid nanoparticles	Nanospheres comprised of the lipid core stabilised by surfactants and/or polymers
	Polymers	Poly-L-lactide-co-glycolide (PLGA) Poly-L-lactic acid (PLA) Chitosan Gelatine	Nanoparticles	Variously shaped structures with all three physical dimensions on the nanoscale (<100 nm)
		Polyamidoamine (PAMAM) Polypropyleneimine (PPI)	Dendrimers	Spherical nanomolecules consisting of the central core and sequential layers of branching groups
Inorganic	Noble metals	Gold Silver Platinum	Nanoparticles	Variously shaped structures with all three physical dimensions on the nanoscale (<100 nm)
	Oxides	Magnetic and superparamagnetic iron oxides	Nanoparticles	Variously shaped structures with all three physical dimensions on the nanoscale (<100 nm)
	Semiconductors	Cadmium Selenium Tellurium Indium	Quantum dots	Semiconductor nanocrystals with optical properties
	Carbon-based	Carbon	Fullerenes	Hollow nanospheres, comprised of carbon atoms, forming cage-like structures
			Nanotubes	Cylindrical structures with two of the three physical dimensions on the nanoscale (<100 nm)
	Other	Mesoporous silica	Nanoparticles	Variously shaped structures with all three physical dimensions on the nanoscale (<100 nm) and mesoporous architecture (pore diameter: 2-50 nm)

evidence supporting the benefits of nanomaterial-based agents in terms of selectivity, sensitivity, affinity and detection limits,[1,9,12] has led to the expansion of nanobiotechnological tools in a number of non-cancer applications, such as cardiovascular,[13] neurological,[14] gastrointestinal,[15] autoimmune inflammatory,[16] infectious[17] and, reproductive diseases, where they are increasingly applied for detection and treatment of cancer and experimental management of non-cancer pathologies.

In this review, we highlight the key benefits of nanotechnology in biomedicine, and discuss its emerging uses in clinical reproductive medicine and experimental reproductive biology, along with the potential areas of future scientific interest. We also address the benefits and concerns associated with the use of nanomaterials in a highly delicate system of reproductive tissues and gametes, and discuss the feasibility of this innovative and potentially controversial approach for reproductive medicine and research into the mechanisms underlying reproductive diseases, including infertility.

Nanomaterials: key features and relevance for biomedical applications

Nanotechnology, in its core, is the science concerning the engineering and application of nanomaterials — natural or manufactured objects with at least one of the three dimensions at the nanoscale (1-100 nm).[18] At this scale, physical, chemical and biological properties of materials fundamentally differ from the properties of single atoms of bulk solid matter, and are controlled by the effects of quantum mechanics, rather than classical physics. Regardless of natural and physicochemical properties, such as size, structure, composition, and shape, nanomaterials are universally characterised by one key feature – the combination of small size and immense surface area. Increased surface energy – and the altered chemical potential of nanomaterials – transforms their mechanical, magnetic, optical, and catalytic properties,[7,19,20] thereby permitting new levels of performance in a variety of industries, including chemical synthesis, energy supply, construction and transportation, food production, data storage and telecommunication, biotechnology, healthcare, and the manufacturing of consumer products.[7]

From the biological perspective, nanomaterials represent highly customisable and robust multifunctional platforms for the non-invasive transport of virtually any type of biological cargo, designed to mark, augment or suppress endogenous functional activity, into a selected target cell population for research, diagnostic and/or therapeutic purposes. Over the last few years, favourable biocompatibility has been demonstrated for a vast array of nanocarriers in combination with a wide variety of mammalian cell types (Table 1; Figure 1). Furthermore, the recent discovery of phospholipid micro- and nanovesicles, naturally produced by mammalian cells and acting as powerful mediators of cell communication *in vivo*, highlights the possibility of manipulating cell function using similar artificial nanostructures.[21,22]

The enormous potential of nanomaterials in biomedicine arises from a number of features, which favour their use in the research and clinical setting (Table 2). Firstly, their small size, comparable to the size of biomolecules, allows straightforward