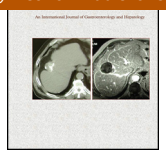
Digestive and Liver Disease 45 (2013) 995–1002

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Review article

Nanotechnology in diagnostics and therapeutics for gastrointestinal disorders

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ARTICLE INFO

Article history:
Received 15 December 2012
Accepted 26 March 2013
Available online 7 May 2013

Keywords:
Diagnostics
Gastroenterology
Nanotechnology
Therapeutics

ABSTRACT

This review describes the state of the art in nanoparticle and nanodevice applications for medical diagnosis and disease treatment. Nanodevices, such as cantilevers, have been integrated into high-sensitivity disease marker diagnostic detectors and devices, are stable over long periods of time, and display reliable performance properties. Nanotechnology strategies have been applied to therapeutic purposes as well. For example, nanoparticle-based delivery systems have been developed to protect drugs from degradation, thereby reducing the required dose and dose frequency, improving patient comfort and convenience during treatment, and reducing treatment expenses. The main objectives for integrating nanotechnologies into diagnostic and therapeutic applications in the context of intestinal diseases are reviewed.

1. Introduction

Nanotechnology is an interdisciplinary research field that integrates chemistry, engineering, biology, and medicine. Several useful nanotechnological applications have been identified in cancer biology, including technologies for the early detection of tumours and cancer biomarkers, and the development of treatment approaches that are impossible to achieve using conventional technologies [1]. The field is rapidly evolving and expanding, and it has gained public and media interest worldwide.

The application of nanotechnology in cancer research has provided hope within the scientific community for the development of novel cancer therapeutic strategies. As gastrointestinal cancers contribute to more than 55% of deaths associated with cancer [2], tremendous efforts have been made towards the development of novel diagnostic and therapeutic methods for improving patient quality of life and lengthening survival. Advances in image-based detection, targeted drug delivery, and metastases ablation could go a long way to improve patient outcome. Classical approaches generally do not meet patients' expectations due to a lack of specificity and poor patient stratification. More highly targeted and customized treatments are needed. Towards this goal, nanotechnologies and nanodevices have been explored for their potential utilities in advancing targeted therapeutic approaches.

Nanotechnology strategies are expected to involve the creation and/or manipulation of materials on the nanometer scale, either by scaling up from single groups of atoms or by refining or reducing bulk materials into nanoparticles (NPs) [3]. NPs are typically several hundreds of nanometers in size and can offer unprecedented interactions with biomolecules on cell surfaces or inside the cell [4]. Extensive types of nanoparticles composed of different materials, shapes, and sizes, and with various chemical and surface properties, have already been engineered (Table 1).

These properties rely on an interaction surface between a target and a NP which is thousands times larger than the interaction surface between a target and a drug. A variety of NPs are used for diagnostic and/or therapeutic purposes in different cancer types. Such NPs assist in visualizing tumours and/or delivering drugs (theragnostic approach) in a targeted manner with reduced toxicity and side effects. Examples of nanodevices developed for use in oncology applications include quantum dots (QDs), carbon nanotubes (CNTs), paramagnetic NPs, liposomes, gold NPs (GNPs), magnetic resonance imaging (MRI) contrast agents for intraoperative imaging, and novel NP-based methods for the highly specific detection of DNA and protein [26–30].

Recent advances have led to the development of bioaffinity NP probes for molecular and cellular imaging, targeted NP drugs for cancer therapy, and integrated nanodevices for early screening and detection of cancer. These developments offer exciting opportunities for the development of personalized therapy, in which the molecular profiles of an individual's genetic and protein biomarkers may be used to diagnose and treat the patient's cancer. Several barriers to the development of in vivo nanodevices applications have slowed progress in the preclinical and clinical stages of development: biocompatibility, in vivo kinetics, tumour-targeting efficacy, acute and chronic toxicity, escape from the reticuloendothelial system, and cost-effectiveness impose high hurdles for nanotechnology [1,31].

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1590-8658/$36.00
http://dx.doi.org/10.1016/j.dld.2013.03.019

Table 1
Comparison of different materials of nanodevices displaying the shapes, the sizes, the properties, and the use of different materials for diagnosis and/or therapeutics.

Material	Size range	Shape	Properties	Applicability	Reference
Fullerene	nm	Nanotubes	Carbon nanomaterials in molecular electronics	Nanowire and biosensor for diagnosis	[5,6]
Carbon nanotubes Polylactic acid Poly(cyano)acrylates Polyethyleinemine Block copolymers Polycaprolactone	1–1000 nm	Spherical	Biodegradable Biocompatible Smart material (external stimuli degradation pH, temperature, . . .)	Drug/gene delivery	[7–13]
Gold nanoparticles	3–100 nm	Spherical	Electronic, optical, and thermal properties	Diagnostics and detection of biological molecules at low concentration	[14–16]
Magnetic nanoparticles	3–100 nm	Spherical	Magnetic properties	Magnetic immunoassays, drug delivery, cell separation, purification, and tissue repair.	[17–19]
Quantum dots	1–10 nm	Spherical	Cd/Zn-selenides	In vitro diagnostic Imaging	[20–22]
Dendrimers	10–200 nm	Complex, branched polymer		Drug delivery systems	[23–25]

Innovation in the field of nanotechnology is required. The field is, therefore, characterized by the continuous growth and evolution in response to these barriers to product development. As a result of these efforts, nanowires, nanocantilevers, quantum dots, nanoshells, dendrimers, liposomes, nanopyramids, and nanogels are used in diagnostic or therapeutic applications in cancer research.

2. Nanotools for diagnostics

2.1. Nanowires for use in diagnostics

Devices based on nanowires provide powerful general platforms for the ultrasensitive direct electrical detection of biological and chemical species [3]. Nanowires may be laid down across a microfluidic channel (Fig. 1), and as particles flow through the microfluidic channel, the nanowire sensors pick up the molecular signatures of these particles and relay the information to a signal analyser. Such systems can detect the presence of altered genes associated with the disease and can help researchers pinpoint the position of these genetic changes [32]. Zheng et al. reported the preparation of a silicon nanowire (SiNW) biosensor array for the simultaneous detection of multiple cancer biomarkers in a single versatile detection platform [33]. The real-time detection of three cancer markers (prostate-specific antigen, carcinoembryonic antigen, and mucin-1) using SiNW biosensors functionalized with three cognate antibodies was demonstrated [34]. The simultaneous high-sensitivity analysis of multiple biomarkers could further facilitate the early detection of cancer [35,36]. This study described the synthesis of aligned ZnO nanowire arrays using a vapour–solid process, as shown in the scanning electron microscopy (SEM) image below. The growth of aligned arrays of nanowires plays an important role in nanobiotechnology and can be used for biosensing, cellular manipulation, and the conversion of mechanical energy into electricity for powering nanodevices. A silicon (Si) nanowire field-effect device was developed in which distinct nanowires and surface receptors were incorporated into arrays [33]. The capacities of Si-nanowire probes for the multiplexed real-time monitoring of protein markers in clinically relevant samples with high sensitivity and selectivity offers the potential for the diagnosis and treatment of cancers [36]. Single-walled carbon nanotubes (SWCNTs) exhibit distinctive electrical and spectroscopic properties, including near-infrared photoluminescence and strong resonant Raman scattering, that may be useful in biological detection and imaging applications [37].

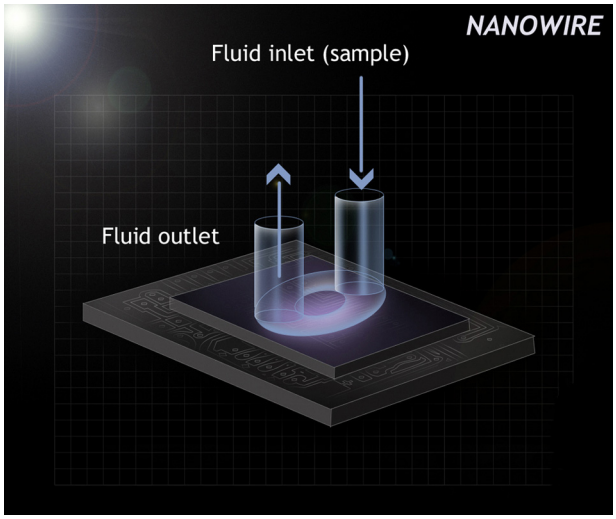

Fig. 1. Schematic of a regular planar nanowire sensor biochip with integrated microfluidic sample delivery. The schematic represents a Si nanowire-based device configured as a sensor potentially covered with receptors and where binding of ligands yields a decrease in the conductance.

2.2. Cantilevers for use in diagnostic applications

The innovative nanocantilever enables the quantitative measurement of low levels of certain molecules. Nanoscale cantilever arrays comprise microscopic flexible beams that resemble a row of diving boards and provide rapid and sensitive detection. The physical properties of the cantilevers change as a result of a binding event and can be read in real-time. A nanocantilever's deflection and resonant frequency may be sensitively modulated by the binding of a surface-immobilized affinity reagent to a biomarker protein or nucleic acid (via hybridization) [37]. For example, an antibody-coated cantilever can selectively bind to one or more specific molecular products secreted by a cancer cell (Fig. 2). This detection can be coupled with modern communication tools (e.g.

Fig. 2. Schematic diagram illustrating an example application of nanotechnology to medicine. (1) Home-based tests, (2) lab-on-a-chip technologies, and (3) cantilever technologies. An patient with inflammatory bowel disease (IBD) undergoing treatment could potentially use a smart phone to send the home-based test results to a server for processing (4), thereby reporting the inflammation marker level status to the patient's physician (5). Such techniques can potentially be used to adjust dosage towards treatment optimization.

smart phones) and provides a customized and real time diagnosis on a disease blood markers. Thus patients will have the unique capability to access in real time their own inflammatory level.

Two equations may be used to describe the behaviour of a microelectromechanical system (MEMS) cantilever. The first is *Stoney's formula*, which relates the cantilever end deflection δ to the applied stress σ:

$$\delta = \frac{3\sigma(1-\nu)}{E}\left(\frac{L}{t}\right)^2,$$

where ν is Poisson's ratio, E is Young's modulus, L is the beam length, and t is the cantilever thickness. Very sensitive optical and capacitive methods have been developed to measure changes in the static deflection of a cantilever beam in a DC coupled sensor.

The cantilever spring constant k is related to the cantilever dimensions and material constants according to the following equation:

$$k = \frac{F}{\delta} = \frac{Ewt^3}{4L^3},$$

where F is the force and w is the cantilever width. The spring constant is related to the cantilever resonance frequency ω_0 by the usual harmonic oscillator formula, $\omega_0 = \sqrt{k/m_{\text{equivalent}}}$. A change in the force applied to a cantilever can shift the resonance frequency. The frequency shift can be measured with exquisite accuracy using heterodyne techniques. Such shifts form the basis for AC coupled cantilever sensors.

Cantilevers are used mainly in the context of atomic force microscopy (AFM). AFM instruments consist of a cantilever with a sharp tip (probe), which is scanned over a specimen surface. The cantilever is typically silicon or silicon nitride with a tip radius of curvature on the order of nanometers. As a tip is brought into proximity with a sample surface, the forces between the tip and the sample produce a deflection of the cantilever according to Hooke's law. Depending on the conditions, the forces measured during an AFM measurement could include the mechanical contact force, the van der Waals forces, the capillary forces, chemical bonding strengths, electrostatic forces, solvation forces, and magnetic forces (see also magnetic force microscopes, MFMs). In addition to these forces, other quantities may be measured using specialized types of probe (see also scanning thermal microscopy, scanning joule expansion microscopy, and photothermal microspectroscopy). Typically, the cantilever deflection is measured using a laser spot reflected from the top surface of the cantilever onto an array of photodiodes. Other detection methods including optical interferometry and capacitive sensing, and piezoresistive AFM cantilevers have also been developed.

AFM techniques provide information about the presence or absence of a compound, as well as the concentrations. The technological breakthrough made by nanocantilevers is made by their extraordinary capacity for multiplexing [38]. In one study, Majumdar used microcantilevers to detect *single-nucleotide polymorphisms* (SNPs) in a 10-mer DNA target oligonucleotide without a need for extrinsic fluorescent or radioactive labels [39]. This application is being explored for applications involving cancer-associated molecules that may be present in very low concentrations. Cantilevers are, therefore, potentially useful tools for the early detection of cancer.

2.3. Quantum dots in diagnostic applications

Quantum dots (QDs) are semiconductor nanocrystals that are readily synthesized and provide characteristic properties that are intermediate between the properties of bulk semiconductors and discrete molecules. The diameters of QDs range from 2 to 10 nm [40]. They display quantized energy levels and size-dependent fluorescent properties [41] (Fig. 3). The fluorescent properties of QDs are suitable for cancer targeting and imaging applications.

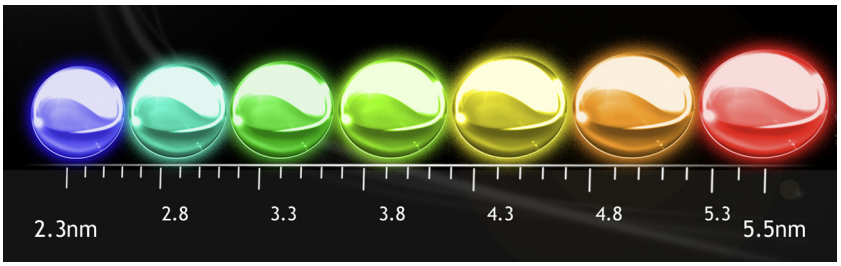

Fig. 3. Illustration of the main optical feature of colloidal quantum dots: their colour. Quantum dots of the same material, but with different sizes, can emit light of different colours. The physical reason is the quantum confinement effect.

Semiconductor nanoparticles can accumulate at a target site due to their enhanced permeability and retention at a tumour site. The targeted accumulation of QDs has been experimentally demonstrated in vivo in a xenograft model involving a human prostate cancer cell line in nude mice [42].

Oncogenes may be detected using a carefully designed series of QDs. QDs with distinct emission spectra may be decorated with distinct specific DNA tags such that an emission spectrum is associated with a specific and unique immobilized DNA tag. The DNA tag-labelled QDs are then incubated with an unknown DNA sample, and the DNA tags hybridize to portions of the sample DNA sequence associated with the disease (the oncogene). Photoillumination of the QDs-tagged DNA results in the emission of a unique bar code, thereby identifying the sequence [39]. This technology was used to develop a method for detecting several molecular markers simultaneously ("multiplexed") in a single tissue specimen. The resulting images of colon tissue were tested as a prognostic marker of the risk of developing colon cancer.

The full spectrum of QDs enables the creation of unique labels that can be used to identify several regions of DNA simultaneously. The versatility of QDs-based methods is important for the detection of cancer, which tends to result from the accumulation of many independent DNA changes within a cell. QDs may be advantageous because administration of a QDs formulation is non-invasive and eliminates the need for a biopsy. QDs toxicity, however, remains a major concern for clinical applications [43–49].

3. Dual nanotools application for diagnostics and therapeutics

3.1. Nanoshells for diagnostic and treatment applications

Nanoshells are miniscule beads coated with gold. The thickness of each layer in a nanoshell may be manipulated towards designing beads that absorb specific wavelengths of light. Due to their size, nanoshells can be injected safely in animal models and preferentially concentrate at cancer lesion sites through a cancer-specific phenomenon called enhanced permeation and retention (EPR). Nanoshells may be used to carry molecular conjugates that can bind to an antigen displayed on a cancer cell surface or in a tumour microenvironment. The application of energy (mechanical, radio frequency, or optical) to these cells from an external source results in energy absorption by the nanoshells. The excited nanoshells then non-radiatively relax to the ground state, producing intense local heating and selectively killing the tumour cells without harming the neighbouring healthy cells. Nanoshells improve the efficacy of a therapeutic treatment and significantly reduce the associated side effects. The most useful nanoshells are those that absorb near-infrared light, which can easily penetrate several centimetres of human tissue.

Fortina et al. [50] proposed a method for the targeted delivery of a therapeutic and the subsequent ablation of colorectal cancer (CRC). In this approach, nanoshells with surface-bound ligands (diarrheagenic bacterial heat-stable peptide enterotoxin, ST) were combined with near-infrared or radiofrequency thermal ablation techniques. The ST targeted surface-bound guanylyl cyclase C (GCC), which is expressed on all normal colonic epithelial cells as well as primary CRC and metastatic tumours [50]. The incorporation of iron or iron oxide into the nanoshell structures provided functionality as a magnetic resonance imaging (MRI) contrast agent.

3.2. Dendrimers for use in diagnostics and therapeutics

Dendrimers are large complex branched polymers with a well-defined structure surrounding an inner core (Fig. 4). The size, shape, branching length, and surface functionalities of a dendrimer may be controlled towards the design of functional nanoparticles [51]. Polyamidoamines (PAMAM) are a set of dendrimers commonly used for the targeted delivery of drugs and other therapeutic agents. Drug molecules may be loaded in the inner core or covalently attached to the periphery of a dendrimer. The most developmentally advanced dendrimer applications have been in the area of MRI or NIR contrast agents for cancer therapies. Surface-modified dendrimer-based nanodrugs have been developed against viruses and bacteria. One such dendrimer-derived microbicide (Vivagel®) was developed to treat HIV and genital herpes. This product relies

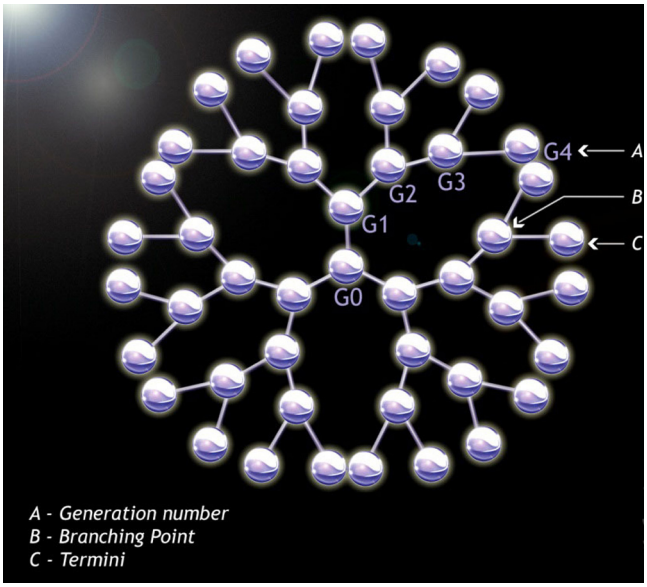

Fig. 4. Schematic of a divergent synthesis of dendrimers. Dendritic molecules are characterized by structural perfection. Dendrimers are monodisperse and usually highly symmetric, spherical compounds and based on successive generation of the same molecule.

on the multivalent properties of dendrimers. The conjugation of antibodies (for example, against CD14 or prostate-specific membrane antigen) to PAMAM dendrimers can provide contrast agents. Such agents have been evaluated using flow cytometry and confocal microscopy methods [52].

Early gene delivery techniques were developed towards the treatment of hereditary diseases; however, the focus has shifted, and current gene delivery approaches are target towards cancers [53]. Certain limitations of gene therapy may be overcome using nanotechnologies. For example, a method was developed to use nonviral delivery vectors, such as liposomes or dendrimers, which are less immunogenic than conventional viral vectors [54]. Nonviral vectors are generally cationic in nature and encapsulate negatively charged DNA through electrostatic interactions. Nanoparticles make good nonviral vector systems because they are safe, simple to use, and easy to produce. Their transfection efficiency is lower than the efficiency of viral vectors, although these deficiencies may be improved using certain structural adjustments, such as the attachment of ligands [55,56]. The dendrimer most commonly used in gene delivery applications is PAMAM, which shows a high transfection efficiency. The transfection efficiency can be further enhanced by heat treatment in water or butanol. Heat treatment increases the dendrimer flexibility, which compacts the dendrimer upon compounding with DNA [57].

3.3. Liposomes in diagnostic and therapeutic applications

Liposomes are widely used in diagnostic and therapeutic application and display outstanding efficiencies in these applications. Liposomes are spherical vesicles comprising an aqueous core surrounded by a phospholipid bilayer in combination with cholesterol. Liposomes can be prepared to have a uniform particle size within the range of 50–700 nm and special surface characteristics [58]. They can be classified by size and by the number of layers present, yielding the following types: small unilamellar, large unilamellar, small multilamellar, and large multilamellar. Vesicle size and shape can change over time, because vesicle preparations are metastable (that is, their structures are not the most thermodynamically stable configuration under the conditions [59]. The circulation time may be increased by attaching polyethylene glycol (PEG) molecules to their surface. PEG molecules protect the liposomes and prevent their clearance.

Important applications of liposomes have been developed in the fields of imaging and drug delivery. Superparamagnetic liposomes are good MRI contrast agents. For example, maghemite particles were introduced into a liposomal vesicle synthesized from egg phosphatidylcholine and distearoyl-SN-glycero-3-phosphoethanolamine-N-[methoxy(poly(ethylene glycol))-2000]. These liposomes were further pegylated. The liposomes were found to be highly efficient contrast agents in the context of magnetic resonance angiography. Here, the liposomes were intravenously injected, and images were collected 24 h after administration [60]. Liposomes have been explored as gene transfer delivery systems. The advantages of liposomes as gene delivery carriers include the facile control over size and the facile modification with a targeting agent. One obstacle to the use of liposomes as gene delivery systems is their low efficiency in the context of DNA encapsulation. The low encapsulation efficiency may be overcome by using cationic liposomes consisting of positively charged lipid bilayers that combine spontaneously with negatively charged DNA via electrostatic and hydrophobic interactions. The transfection efficiency has been improved by mixing the liposomes with cholesterol and further modifying with functional ligands [61].

3.4. Nanopyramids

Electrochemical deposition offers a useful method for generating different nanodevices shapes [62]. Several particle morphologies, including rod-like or dendritic gold nanostructures, have been obtained in a one-step process without a template and typically in the presence of an additive, such as Pb^{4+} or cysteine. However, those nanostructures were not necessarily well defined. The non-templated electrochemical fabrication of pyramidal, rod-like, and spherical gold nanostructures on a sputtered gold film usually proceeds in a single step and is inexpensive. Researchers at Northwestern University have fabricated gold nanopyramids that can be positioned on silicon pedestals [63,64]. When illuminated with light, the anisotropic nanopyramids generate heat. Nanopyramids may be taken up by cancer cells, which tend to have "leaky" cell walls, and localized heating (using near-infrared illumination) results in cell death.

3.5. Nanogels

Nanogels (NGs) are nanoscale hydrogels composed of polymer chains that are cross-linked via noncovalent interactions or covalent bonds [65,66]. NGs have attracted much attention because they are sensitive to external stimuli by changing their volume and shape much more rapidly than macroscopic gels [67,68]. NGs can accommodate a variety of molecules in their inner free spaces [69–71]. The elasticity of a NG significantly affects its biodistribution [72]. An example of nanogels application was described by Cheng et al. [73], who used nanogels to target human umbilical vein endothelial cells (HUVECs) in a model cell system. The targeting capacities of zwitterionic poly(carboxybetaine methacrylate) (pCBMA) nanogels conjugated to cyclo[Arg-Gly-Asp-D-Tyr-Lys] (cRGD) were tested, and pCBMA was found to selectively bind to HUVECs expressing Rvβ3 or Rvβ5 integrins.

4. Imaging and detection in colorectal cancer

Beyond imaging and detection applications, targeted nanostructures may be used to develop novel approaches for the treatment of colorectal and other tumours [74]. Currently, the nodal status of a colorectal cancer can only be reliably determined by histopathological examinations of a resected specimen. New methods for intra-operative staging would guide surgical resection according to the disease stage.

Nanostructure-based MRI contrast agents exhibit great potential for use in the in vivo imaging and diagnosis of colon cancer. Nanostructures may be used to modify conventional contrast agents, such as gadolinium, or imaging agents, such as iron oxide, in an effort to enhance the diagnostic power of clinical imaging [75–79]. Not only do these nanostructures improve the features observed in conventional MRI imaging, they present an opportunity to alter the methods used to detect and manage colorectal cancer.

4.1. Endoscopy NIRF using QDs

Near-infrared fluorescence imaging (NIRF) shows promise as a new modality in CRC imaging. NIRF can be used to image gastrointestinal diseases, such as CRC, because the current clinical evaluation of CRC involves fibre optic examinations of the luminal surfaces [74]. Intra-operative fluorescence using naturally fluorescent biomarkers or fluorescent tumour probes may offer a practical means for intra-operative lymph node staging. Nanotechnology may potentially enhance the use of such fluorescent probes. The standard of care may be improved by better endoscopic visualization techniques using near-infrared fluorescence imaging agents,

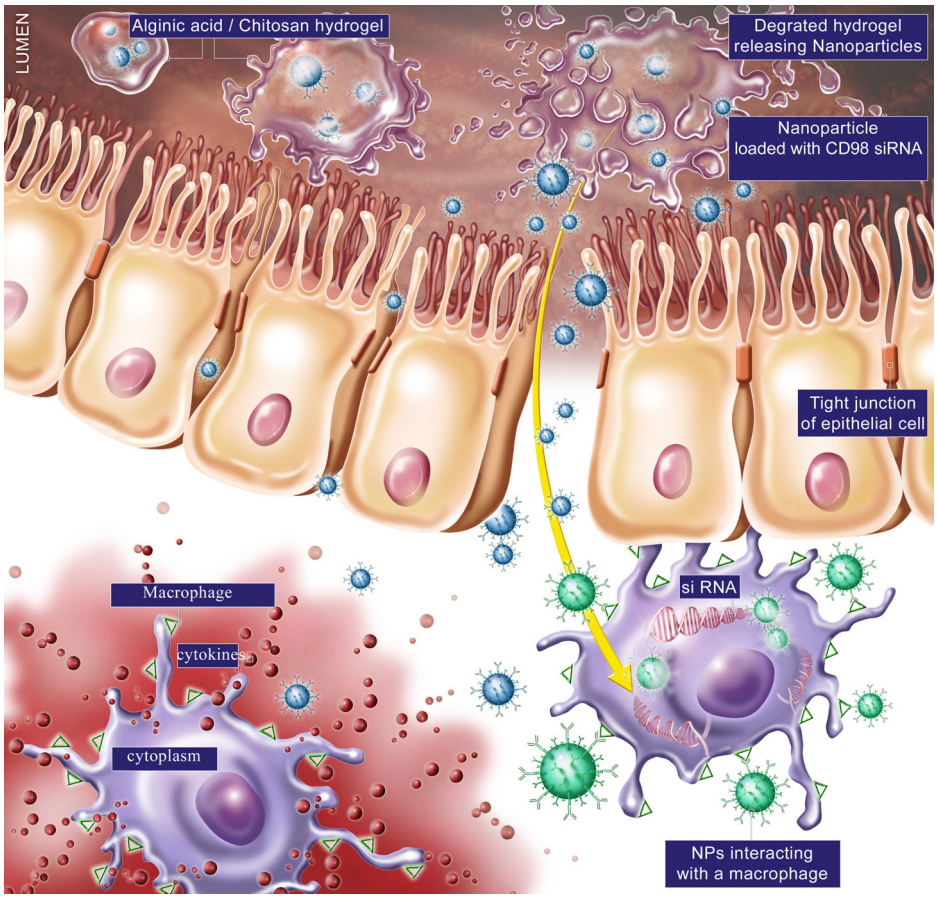

Fig. 5. Illustration representing the nanoparticles (NPs) in targeted strategy. With oral intake of NPs encapsulated in a hydrogel, the bioactive component is distributed specifically in the colon. In targeting strategy, NPs are covered with an antibody whose ligands are overexpressed in inflamed areas. The NPs accumulate and the drug is released in the specific area.

such as tunable quantum dots. Indeed, a murine model of colon cancer has been studied using a NIRF agent [80].

4.2. Gastrointestinal delivery of anti-inflammatory nanoparticles to treat inflammatory bowel disease

The advantages of using nanostructured vectors in drug delivery systems are numerous. Nanostructured vectors reduce the severity and incidence of side effects by lowering the required drug dose, and they increase the interaction specificity between a drug and its target. Specific targeting is more efficient and less costly than systemic therapies [81]. The colon is the targeted organ in inflammatory bowel disease mainly, including ulcerative colitis and Crohn's disease. A large number of drugs may potentially be loaded into nanoparticles (NPs). Small molecules, such as tripeptides [7] and siRNA [9], or larger molecules, such as proteins [10] (hormones or antibodies), may be encapsulated alone or in a complex form inside a NP (Fig. 5). NP synthesis and loading with anti-inflammatory compounds was immediately followed by delivery to the colon. An efficient technique was developed for specific targeting of the NPs to regions of the digestive tract, including colon, using a hydrogel held together by electrostatic interactions between positive ions and negative polysaccharides. The in situ double cross-linking of chitosan and alginate, mediated by Ca^{2+} and $SO_4{}^{2-}$upon administration to a mouse gastrointestinal (GI) tract by double gavage, provided gel formation. A drug was encapsulated within NPs, the NPs were targeted to the colon, and its degradation was avoided under the harsh environmental conditions of the GI tract. The combination of biomaterials (hydrogels) and nanostructures enabled dose reduction and the efficient loading and delivery to the colon, where the release of drug reduced colon inflammation [7,9,10,81,82].

5. Conclusions

Nanostructures and nanotechnology-based devices are under active development towards the design of diagnostic and therapeutic tools and devices. Nanoparticles have a size of the order of 1–100 nm and can be functionalized to display specific properties at the cellular, atomic, and molecular levels. Rapid innovations and improvements have led the field through continual changes. The use of nanotechnology in biomedical research and clinical practice has defined the field of nanomedicine, which has the potential to have a major impact on human health. Nanomaterials are increasingly used in diagnostic, imaging, and targeted drug delivery applications. Nanotechnology promises to facilitate the development of personalized medicine, in which patient therapy is tailored by the patient's individual genetic and disease profile. This review provides an overview of nanotechnology applications in molecular diagnostics and drug delivery. The coupling of nanotechnology strategies and telecommunication will improve the precision of diagnostics and therapeutics (Fig. 2) and promise to impact the care and management of diseases such as intestinal diseases and cancer.

In the near future, medical approach and diagnostics will certainly dramatically change. Nanoscale sensors and devices may provide a personal and cost-effective continuous medical monitoring of patient's health. Nanoscale sensors and devices may

also support an enhanced prediction in early stage of diseases such as cancer or inflammations. Future sensor systems will be able to use multiple physical phenomena to sense many analytes (biomarkers) simultaneously. Further future perspectives include technology miniaturization which will allow association of nanotools (NPs, liposomes, quantum dots, etc.) with nanodevices (nanowire, biochips, etc.); this will allow novel measurements such as an optical transducer for light; an electro/chemical transducer for electrical properties; a magnetic transducer for changes to local magnetic fields; and a mechanical transducer, to detect changes in motion.

Conflict of interest statement

The authors disclose no conflicts.

Acknowledgments

This work was supported by grants from the Department of Veterans Affairs and by the National Institute of Diabetes and Digestive and Kidney Diseases (National Institutes of Health) through grant RO1-DK 071594 and RO1-DK-064711 (to D.M.) and grant K01-DK097192 (to H.L.).

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