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REVIEW

Nanopharmacology in translational hematology and oncology

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Abstract: Nanoparticles have displayed considerable promise for safely delivering therapeutic agents with miscellaneous therapeutic properties. Current progress in nanotechnology has put forward, in the last few years, several therapeutic strategies that could be integrated into clinical use by using constructs for molecular diagnosis, disease detection, cytostatic drug delivery, and nanoscale immunotherapy. In the hope of bringing the concept of nanopharmacology toward a viable and feasible clinical reality in a cancer center, the present report attempts to present the grounds for the use of cell-free nanoscale structures for molecular therapy in experimental hematology and oncology.

Keywords: hematological malignancies, nanoparticles, translational medicine

Introduction

Nanopharmacology is an interdisciplinary research field, which was developed as an interaction between chemistry, engineering, biology, and medicine, and it is currently receiving growing interest in the clinic.[1] Progress in nanotechnology has gained attention in recent years by developing novel nanoparticle-based drugs or by discovering novel applications in early diagnostic or prognostic assays in cancer.[2] Multiple preclinical studies aim to improve the therapeutic index of a patient diagnosed with cancer using a wide range of nanostructures including carbon nanotubes, peptides, nanodiamonds, cyclodextrine, graphenes, liposomes, quantum dots, nanowires, and metal-based nanoparticles.[3,4]

The latest advances in nanotechnology have brought various options that could be used in the clinic by employing constructs for molecular diagnosis, disease detection, cytostatic drug delivery, and nanoscale immunotherapy.[5–8] The United States Food and Drug Administration has approved the use of liposome-encapsulated doxorubicin (Doxil®; Janssen Products, LP, Johnson & Johnson, New Brunswick, NJ, USA) and paclitaxel attached to nanoparticles (Abraxane®; Celgene Corporation, Summit, NJ, USA)[9,10] in cancer therapy.

In this review, we present the latest investigation on nanostructure systems with applications in hematology and oncology. The latest advancements in nanopharmacology lead to heightened expectations concerning their application in diagnostics, therapy and imaging.

Drug nanocarriers in cancer pharmacology

In the last few years, our team has shed a new light on the field[11,12] by different conjugation procedures for these therapeutics. Overcoming this threshold bears major clinical significance in oncology and hematology, as developing nonviral gene delivery vehicles will bring new patient-tailored drugs within reach (Figure 1). The transport of therapeutic nucleic acids through the cell membrane is inefficient mainly

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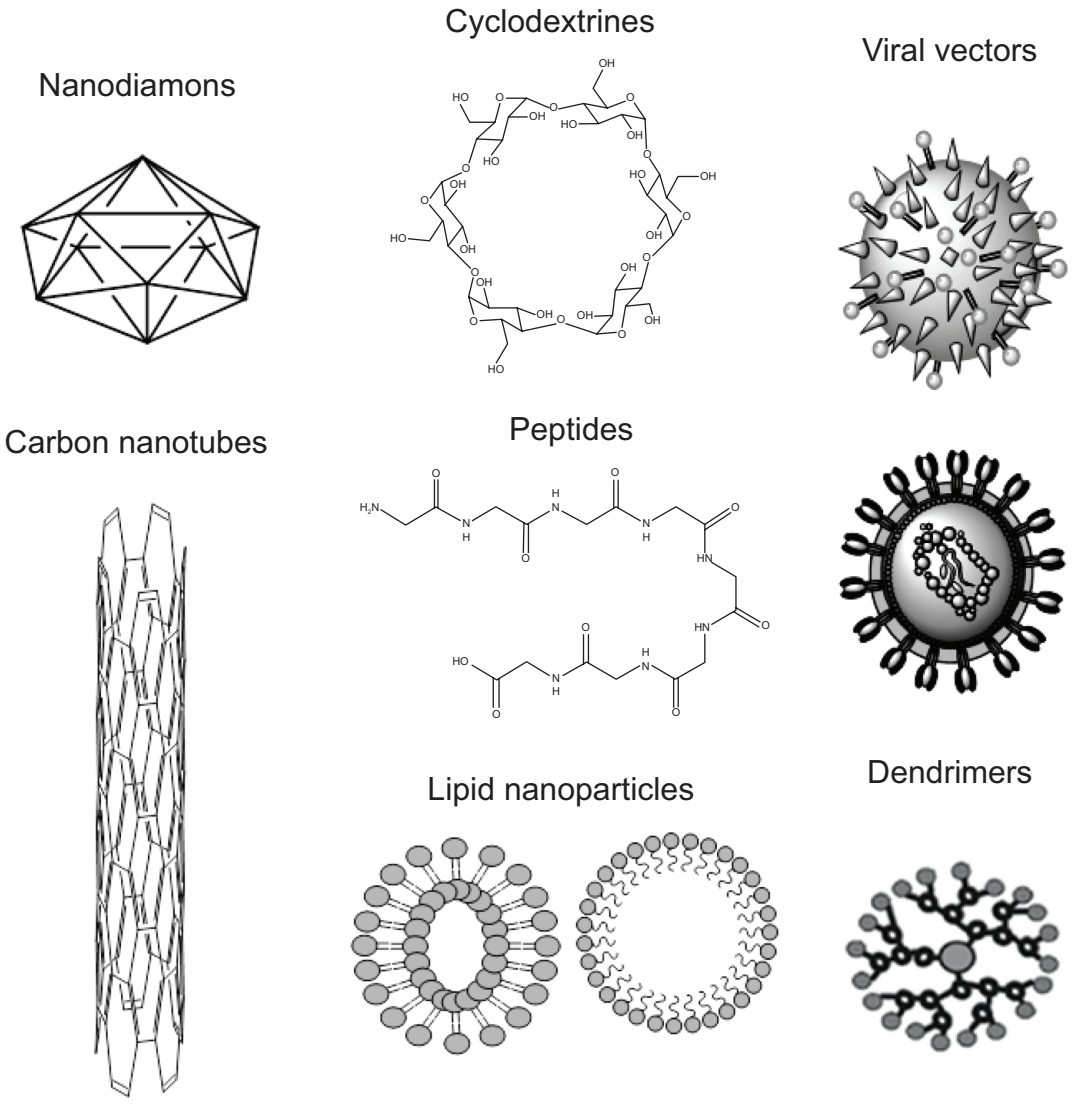

Figure 1 Nanoparticles used in medicine.

in experimental models and includes antisense or antigene oligonucleotides, short interference ribonucleic acid (siRNA) or micro ribonucleic acids (miRNA).[13,14]

Surgical resection in early tumor stages is the main therapeutic option for most solid malignancies, yet therapeutic benefits are frequently modest because of the high rate of tumor recurrence.[15] Chemotherapy and, more recently, molecular therapy, were proven to offer much more efficient therapeutic approaches for patients diagnosed with cancer.[2] Nevertheless, these options are most often accompanied by important systemic side effects associated with the active agent, making a direct delivery the most "elegant" and efficient therapeutic option. The direct delivery of chemotherapy drugs aims to achieve high concentrations of the cytostatic agents at the target site with minimized risk of systemic toxicity (Figure 2).[16]

In cancer chemotherapy, the clinician aims to achieve a good therapeutic index, which is the ratio of the lethal dose for 50% of the population to the minimum effective dose for 50% of the population.[17] However, cancer is most often characterized by multidrug resistance (MDR) and thus scientists have developed new ways to target the MDR cells.[18] MDR cells are known to be frequently located in hypoxic areas, distant from any blood supply, thus overcoming the natural barrier of drug efflux pump activity.[18] Such smart molecules may increase the drug's bioavailability and transform an active agent from a low therapeutic candidate into a highly efficient drug. A wide variety of both organic and inorganic substances are used for engineering nanostructures, such as liposomes, micelles, nanoemulsions, polymers, quantum dots, gold, iron oxide, and even dendrimers.[19–22] All these structures were developed in order to have a large surface area, making these

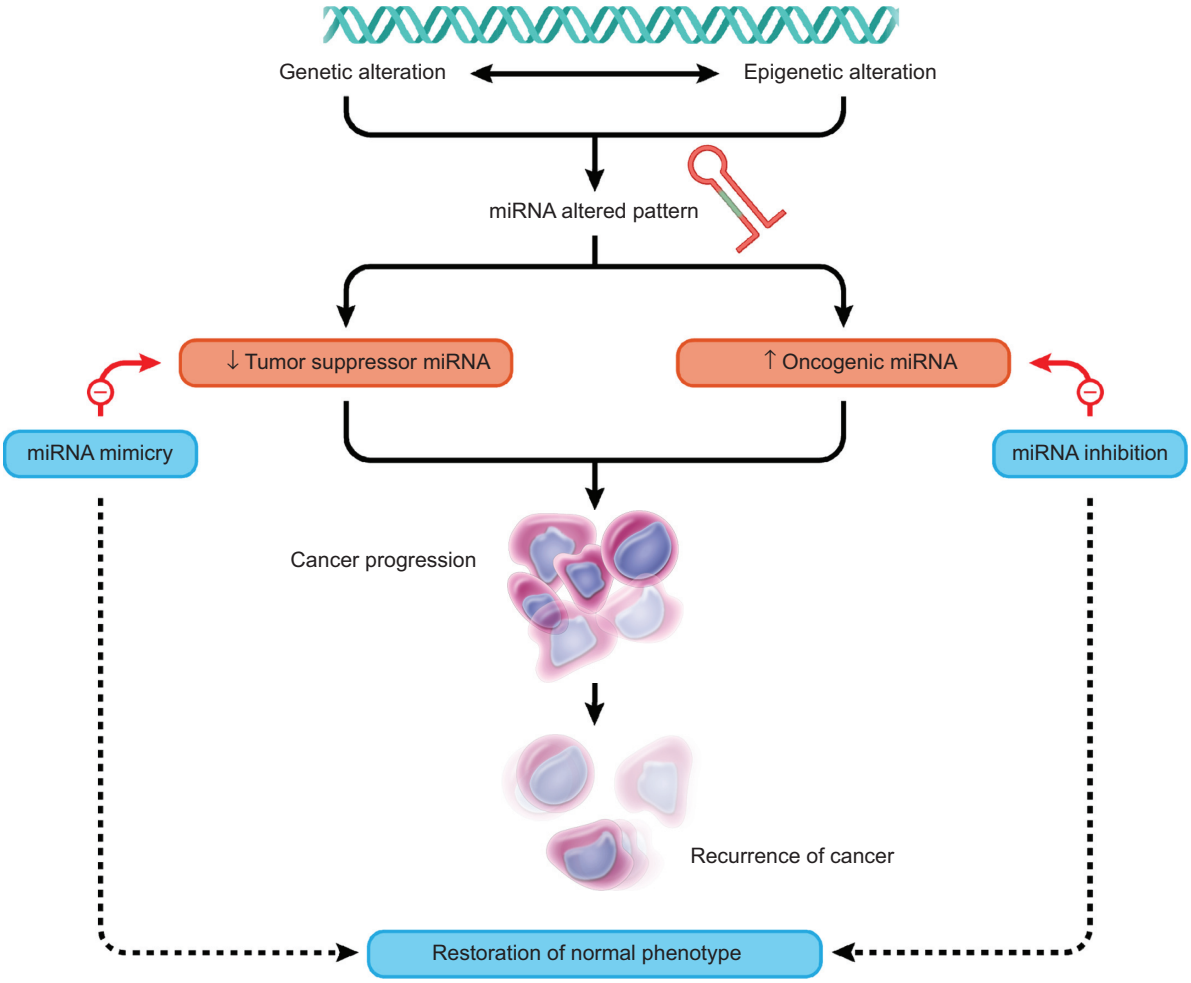

Figure 2 miRNA-based approaches in cancer therapy.
Abbreviation: miRNA, micro ribonucleic acid.

particles suitable for suspension storage, as well as high drug encapsulation and extensive surface absorption capacity, which are pharmacokinetic features that are found in any current structure used in classical pharmacology.[23] However, the most important aspect, especially for cancer, is that nanocarriers are able to bypass the extracellular efflux activity of the adenosine triphosphate-binding cassette transporters in order to be internalized via nonspecific endocytosis,[24–26] such as the case of immunoliposomes[27,28] and poly (butyl)-cyanoacrylate nanoparticles.[29,30] At the same time, the nanocarriers use surface charge-switchable polymeric magnetic nanoparticles as a safe delivery system.[31–33] In this way, the active agent is released near the nucleus, far away from the membrane-bound P-glycoproteins, which is of paramount importance when trying to overcome the resistance to conventional chemotherapy of cancer stem-like cells.[34–36]

Ozeki et al[37,38] have experimented with a new drug delivery model in malignant gliomas. They managed to bypass the blood–brain barrier by using a unique thermo-reversible hydrogel, composed of drug/poly(lactic-co-glycolic acid) (PLGA) microspheres. This thermo-reversible polymer is a gel at body temperature and a sol at room temperature – conditions in which the drug/PLGA microspheres dispersed in the polymer are injected into the human body. Following the procedure, a gel forms around the injection site; this keeps a high concentration of the active substance in the tumor, preventing its dispersion in adjacent healthy tissues.[39] Devalapally et al[40] used poly(epsilon caprolactone) nanostructures whose surface has been modified with poly(ethylene glycol) (PEG) before being loaded with tamoxifen and paclitaxel for the treatment of multidrug-resistant cancer cells. The results were encouraging, as this combination resulted in a lower therapeutic dose of the cytostatic agent, with important clinical applications regarding chemotherapy-related side effects.

The first groundbreaking drug was doxorubicin encapsulated in circulating liposomes (Doxil) for the treatment

of Kaposi's sarcoma in patients diagnosed with acquired immunodeficiency syndrome (AIDS).[41] Recently, this therapeutic option has been applied for other cancers such as breast cancer, since doxorubicin encapsulated in liposomes induces a twofold increase in intracellular drug levels when compared to standard doxorubicin treatment.[42] Doxil is a PEGylated liposomal drug that has a 100 nm diameter in order to prevent the interaction with plasma proteins such as opsonins and high-density lipoproteins (HDLs) and low-density lipoproteins (LDLs), or to avoid elimination by macrophages.[43–45] After the conjugation of a liposome with PEG (a process called PEGylation), the new drug can stay in the systemic blood flow for longer periods of time due to the development of an aqueous layer on the surface of the liposome, leading to a lack of immune recognition and rejection.[46,47] This results in the stabilization of the lipid bilayer and steric hindrance, with important consequences such as decreasing protein absorbance and recognition by the host's macrophages.[48] Many reports show the ability of various gold/silver nanoparticles or carbon nanostructures to enhance the antitumor effect of certain drugs.[23] However, in hematology, HDL nanostructures target the scavenger receptors (B1) and promote cholesterol efflux in lymphoma cells.[49] Indirectly, these exogenous lipoproteins inhibit lymphoma growth and invasion by starving the malignant cell,[50,51] thereby aiding the classic chemotherapy regimen.

PEGylated liposomes loaded with docetaxel, and prepared using the thin film hydration method, showed enhanced in vitro cytotoxicity against A549 and B16F10 cells when compared to Taxotere® (Sanofi-Aventis, Bridgewater, NJ, USA).[52] The capacity of a self-nanoemulsifying drug delivery system was assessed in order to increase the bioavailability of docetaxel and, consequently, its therapeutic activity.[53] This study showed that a self-nanoemulsifying drug delivery system exhibited superior efficacy with low associated toxicity when compared to the commercialized formulation of this bioactive agent (Taxotere).[53]

In recent years, gold nanoparticles have also emerged as therapeutic options for the targeted delivery of antineoplastic active substances, due to their special chemical and physical properties such as functional versatility, biocompatibility, and low toxicity.[54–56] Apart from being of small size (30–50 nm in diameter),[57] naked gold nanostructures have a plasmon absorption in the near-infrared region and display strong photothermal ability. These structures lack a silica core, have a spherical shape, and have a strong and tunable absorption band between 550 nm and ~820 nm.[58–61] These properties make them highly efficient carriers of various drugs already used in the clinic. Their effect has already been shown by our team in malignant gliomas and hepatocellular carcinoma for temozolomide, cisplatin, doxorubicin, and capecitabine.[62]

Diamonds can provide a very efficient delivery system for some chemotherapy agents. In the last few months, nanodiamonds have emerged as potential carriers in neuro-oncology or hemato-oncology. Xi et al[63] have conjugated nanodiamonds with doxorubicin and used convection-enhanced delivery for supratentorial tumors in a murine model. Man et al[64] have also used nanodiamonds to deliver another type of anthracycline to multidrug-resistant malignant cells. They showed that acute myelogenous leukemia, often leading to patient death in the clinic because of resistance to chemotherapy, might be managed by a nanotechnology-based targeted delivery of daunorubicin to the hematological malignancies. Camptothecin is a natural hydrophobic anticancer drug that could be potentially used for breast adenocarcinoma management if delivered correctly at the tumor site.[65] Delivery can be achieved using nanotechnology, as is the case of the self-assembling peptide amphiphile nanofibers. Soukasene et al[66] proved this concept in a mouse orthotopic model of breast carcinoma. Camptothecin was also confirmed by Min et al[67] to be efficient in breast chemotherapy when delivered to malignant cells, by encapsulating it in modified glycol chitosan nanoparticles, thereby achieving a high concentration with minimal side effects in healthy tissues, after having used subcutaneously implanted xenografts in immunocompromised mice. Since monoclonal antibodies are increasingly used in clinical oncology, some investigators have tried to add the targeted effect of antibody-based drugs to a nanocarrier in order to obtain maximum anticancer effects with minimal side effects.[2,23] Thus, trastuzumab was conjugated with various nanostructures, including carbon nanotubes or nanospheres.[68] The desired effect was achieved and, in the near future, we may expect newly described cytostatic agents in Phase I or Phase II clinical trials.

Immunotherapy is a very important part of the multimodal approach in cancer management. The immune system may also influence the outcome of a certain regimen. Ni et al[69] have applied this concept by developing a local vaccine after conjugating graphene oxide targeting interleukine-10 receptor. Thus, the anti-inflammatory action of interleukin-10 is blocked and the suppressive tumor microenvironment becomes a target for the immune system.

Nanovectors can be used as carriers for drugs, but also for contrast substances, with a high applicability in diagnostic medicine.[70] Iron oxide, gold, gadolinium, or even quantum

dots represent good alternatives for radiation oncology, photodynamic therapy, or hyperthermia.[71,72] Iron oxide has important superparamagnetic characteristics and is one of the most investigated nanostructures in diagnostics, including in lymph node imaging, the inhibition of cancer cell dissemination and stem cell trafficking, visualization of ribonucleic acid (RNA), interference and T-cell-specific labeling.[73–77] As a contrast agent, iron oxide is especially useful for magnetic resonance imaging (MRI), and it is very sensitive in detecting solid tumors, but it has little or no applicability in lymph node micrometastasis or hematological malignancies.[78,79] While still in the early stages, the research in this field will more than likely improve in the near future. In prostate cancer, Harisinghani et al[78] have already proven that the use of iron nanostructures as a contrast agent in MRIs detects over 90% of all lymph node disseminations, which is in comparison with the detection rate of 35% in classic MRIs.

Even though chemotherapy remains the most widely used and effective treatment option for disseminated malignancies, acquired or intrinsic drug resistance accounts for almost 90% of treatment failure. MDR represents the simultaneous resistance to various medications that are different both structurally and functionally, most often as a result of the drug efflux pumps that reduce the intracellular levels and thus reduce the cytotoxic effect on the cancer cell.[6] New nanotechnology-based theranostics are evolving and are expected to confer new strategies in overcoming the drug efflux transporters, which are findings that are presented further in the next section. The multifunctional characteristics of the nanocarriers make them very suitable for treating a heterogeneous tumor mass in comparison to classic approaches.[15] Nanocarriers have a preferential accumulation within the malignant cell due to the enhanced permeability and retention effect.[23,80] Thus, the drug concentration is increased in the malignancy and reduced in the surrounding, healthy tissue. This will result in an increased efficacy of systemic therapy, with decreased side effects.[23,70]

Nanotechnology can be applied not only in chemotherapy, but also in radiation oncology, by combining radiobiology with experimental pharmacology. Malignant cells are sensitive to ionizing radiation emitted by various radioactive metals.[81] By delivering such substances to the primary tumor site, we may improve current radiotherapy or brachytherapy protocols. Chanda et al[82] have conjugated gum arabic glycoproteins to gold nanoparticles and tested this new assay on a murine model of prostate cancer. The administration of a single dose of beta-emitting irradiation increased the local administered dose up to 70 Gy and induced the regression of prostate adenocarcinoma in nude mice. Garrison et al[83] also used an in vivo murine model of prostate cancer and demonstrated that beta radiation emitting bombesin could be used to specifically target cancer cells.

Nanocarriers conjugated with miRNAs or anti-miRNA oligonucleotides

The human body has natural barriers for preventing a wide range of diseases, whether considering the organism/body level, the tissue–organ level, the cellular level, or even the molecular level. Thus, the simple aim of achieving highly localized drug delivery with maximal anticancer effects and minimal side effects is very troublesome, as it can be expensive, time consuming, and it does not offer any guaranteed success.[2,23] This emphasizes the need to design highly specific carriers that can deliver highly specific active agents in order to achieve maximum efficacy with minimal toxicity. In vivo, various miRs can be delivered either by viral or nonviral carriers, depending on transfection efficiency, the safety of the receiving host, immunogenicity, or side effects.[84,85] Nonviral carriers are nonetheless considered to be more suitable in the clinic, especially cationic transporters such as PEG. This is because it has a strong buffering ability and it can release functional genetic material into the cytosol after having induced osmotic endosome breakage.[86–88] The main disadvantage is that PEG is not cell-specific, and one would need very high doses in order to achieve the desired concentration, leading to potentially serious side effects.[89,90] Thus, the need to improve current knowledge in the field and to produce other ligand molecules for aptamers functionalization. Aptamers are short, single-stranded oligonucleotides formed by 30–50 bases and they express minimal or even no antigenicity and immunogenicity, making them more suitable for in vivo use in clinical hematology and oncology.[91–93]

Other nonviral vector systems may also include carbon nanomaterials, such as nanotubes or fullerenes. Our studies used nanotubes because of their unique intrinsic physical and chemical properties in an attempt to deliver siRNA in hepatocellular carcinoma cells.[12] The molecular analysis of the experiments has proven that p53, TNF-α, and VEGF levels were altered after siRNA transfection. This proves that carboxylated carbon nanotubes may provide an alternative to the lipid transfection system-based therapy for liver malignancies. The successful functioning of the endosomal siRNA system and followed by the release of the RNA molecules into the cytoplasm are very important for the efficient use of oncogene silencing.[1,2,13] In order for this process to be

carried out with minimal side effects, tertiary complexes were developed out of nucleic acids, polycations, and a charge-reversal polymer that can pH-dependently alter its electric charge either into the positive or negative state.[94–96] When the vector arrives into an organelle such as an endosome or a lysosome, both are known to have a pH of 5–6, the charge conversion facilitates endosomal escape through a membrane disruption process after having enhanced the so-called "proton sponge".[97–99] Apoptosomes represent other models of molecular self-assembly structures. In such wheel-like structures, an individual Apaf-1 protein will form a complex with cytochrome-c[100] before recruiting and activating procaspase-9.[101] This will trigger a cascade of other events, which may lead to apoptosis. Polymeric micelles are artificial structures that resemble apoptosomes and act as either drug solubilizers or carriers of antisense oligonucleotides and drug molecules.[102] A single-stranded oligonucleotide can recognize a target molecule on a cancer cell both through Watson–Crick base pairing with folic acid, and also through hydrophobic interactions and hydrogen bonding.[103] Such an oligonucleotide ligand is also known as an aptamer, which has very important properties that include its small size, a lack of immunogenicity, and ease of synthesis.[104,105]

Exosomes are vesicles ranging from 30–90 nm in diameter, and they are known to play a key role in intercellular communication.[106,107] This communication is accomplished using various cytokines, interleukins, and a substantial amount of RNA.[108] RNA carried by the exosomes is mostly a RNA and miRNA messenger, with very little 18S and 28S ribosomal RNA.[109,110] Since exosomes are used in normal cell physiology in RNA transport, researchers have attempted to use these nanostructures in gene therapy as a vector to deliver therapeutic nucleic acids to target cancer cells.[108,111] Gene therapy aims to provide a therapeutic solution for the cause of the disease, rather than for its symptoms. Two types of vectors (either viral or nonviral) are currently available in the US, according to an online search of the National Institutes of Health database (http://clinicaltrials.gov/ct2/home). Most of the 262 ongoing trials use viral vectors, yet this approach is associated with a high toxicity and an important immunological response from the host organ. Exosomes are far more efficient because they can target cancer cells and trigger little or no immune response since they are isolated from the patient's bodily fluids and are subsequently transferred back to the same patient after an insertion or deletion of the genetic material in vitro.[112–114] Wahlgren et al[115] used exosome-delivered siRNA in order to achieve posttranscriptional gene silencing. They showed that the MAPK-1 protein was downregulated in both monocytes and lymphocytes that were cocultured with particles, which were genetically modified to carry an anti-MAPK-1 transcript.

Exosomes represent an important delivery system,[116,117] which proved its efficacy in vitro for RNA and protein transport.[118] A good therapeutic effect with low immunogenicity was observed for siRNA.[1,2,13] In a study conducted by Alvarez-Erviti et al[119] the capacity to downregulate the BACE1 protein and messenger RNA levels was demonstrated using exosome-mediated siRNA delivery produced by dendritic cells. The same group[119] has also engineered dendritic cells to express the exosome-specific protein, Lamp2b, fused with the peptide, rabies virus glycoprotein, which is specific for neuronal lineage cells. Thus, dendritic cells synthesized exosomes, which were loaded to exogenous siRNA. This resulted in the knockdown of BACE2. The clinical implications are of great potential in the management of Alzheimer's disease.[120] Gold is a noble metal used throughout the ages of human history in all aspects of civilization, including in medical science,[121,122] and nanotechnology-based new approaches make no exception. Polyvalent oligonucleotide-functionalized gold nanostructures have been designed to enter cancer cells without the use of a cationic cocarrier after having been functionalized with a synthetic miR sequence. The prototype of the miR mimic-gold nanoparticle construct consists of a 1–15 nm gold nanoparticle, which was functionalized with a monolayer of a double-stranded alkylthiol-modified RNA molecule of around 30 duplexes.[123] Hao et al further proved that a gold nanostructure could carry the mimics of miR-205, which are known to have a tumor suppressive effect, thus inhibiting cancer cell proliferation and migration.[123]

miRNA-based therapy

miRNAs are able to modulate different pathways,[124,125] taking into account that a single miRNA is able to target multiple genes. Various approaches were applied to assess the significance of a particular miRNA or distinct representatives from a miRNA family, while noting that miRNAs from the same family could have antagonistic biological effects.[126,127] There is increasing evidence that attempts to explain the miRNA's observed correlation with drug sensitivity.[128–130]

The practical implication of miRNAs in the initiation, development, and progression of cancer has led to the buildup of novel therapeutic schemes. Approaches include, among others, the inhibition of upregulated miRNAs (oncogenic role), as well as using miRNA replacement therapy by restoring the normal levels of tumor supressors miRNA. Oncogenic

miRNAs are inhibited based on antisense oligonucleotides, antagomirs, sponges, or locked nucleic acid structures.[118] Additional approaches involve the restoration of tumor suppressor miRNA expression using miRNA mimics, based on viral or nonviral delivery systems. Both approaches have showcased favorable outcomes in preclinical and clinical studies.[118]

Considering the significance of miRNAs in cancer and its capacity to modulate various biological pathways, miRNA mimics/inhibition asserted a new and effective therapeutic strategy in cancer.[1,2,118] Specifically, miRNAs or anti-miRNA may be used individually or in combination with chemotherapy, leading to an enhanced therapeutic response and to an improved survival rate.[131] In order to apply the vast potential of miRNAs for therapy, the main obstacle for the successful translation of therapeutic strategies into the clinic remains the pathway of delivery.[132]

miRNA expression patterns can be altered by various mechanisms, including genetic and epigenetic alterations.[133] Correlations between miRNA expression and chromosomal abnormalities were shown to be involved in the pathogenesis of chronic lymphocytic leukemia, since miRNAs are involved in the initiation, prognosis, and chemoresistance of chronic lymphocytic leukemia.[134–136] Concomitantly, the inhibition of the oncogenic miR-21 with antisense oligonucleotides generates a proapoptotic and antiproliferative response in vitro in different cell models, reducing tumor development and metastatic potential in vivo.[118] Other examples are presented in Table 1.

Clinical implications in hematology and oncology

Nanotechnology is of major interest in clinical hematology and oncology for both therapy and diagnosis because of their

Table 1 Examples of miRNA therapeutic implications in hematological malignancies

Hematological disease	Study model	Target miRNA	Biological effect	Reference
MCL	MCL cell line; xenograft MCL mouse model	miR-17-92 cluster	Protein phosphatase PHLPP2, a key negative regulator of the PI3K/AKT pathway, being a target of miR-17-92	118,137,138
AML	OCI-AML3 and Molm13	let-7a	CXCR4 regulates let-7a expression via YY1, leading to the activation of MYC and BCLXL in AML cells	139
	AML versus healthy individuals	miR-221/222	miR-221/222 can be considered a marker of disease progression and an important therapeutic target	140
	AML cell lines, mouse models, and primary samples	Mir-29	Target apoptosis, cell cycle, and proliferation pathways; reduce tumorigenesis	141
	AML versus healthy individuals	miR-155	miR-155 upregulation identifies high-risk patients	142
ALL	Reh cells, ALL primary cells	MiR-125b, miR-100, and miR-99a	Coregulate vincristine resistance in childhood ALL	143
CLL	MEG-01 cells; tumor xenografts of leukemic cells in nude mice and in primary CLL samples	miR-15 and miR-16	miR-15 and miR-16 induce apoptosis by targeting BCL2	144
	CLL samples in animal models	miR-29 and miR-181	miR-29 and miR-181 are inversely correlated with *TCL1* expression	145
CML	Imatinib-resistant versus imatinib-responsive patients	miR-181c	miR-181c target genes like *PBX3*, *HSP90B1*, *NMT2*, and *RAD21* were correlated with drug response	146
	K562 cells, CML patients versus healthy individuals	miR-196b	miR-196b downregulation increase the expression of *BCR-ABL1* and *HOXA9* oncogenes	147
	K562 cells, CML patients versus healthy individuals	mRNA-30a	mRNA-30a downregulation leads to increased *ABL1* and *BCR-ABL1* expression	148

Abbreviations: miRNA, micro ribonucleic acid; MCL, mantle cell lymphoma; PI3K, phosphoinositide 3-kinase; AML, acute myeloid leukemia; CXCR4, chemokine receptor type 4; MYC, myelocytomatosis oncogene; BCLXL, B-cell lymphoma–extra large; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; MEG-01, maternal-effect germ; BCL2, B-cell lymphoma 2; CML, chronic myeloid leukemia.

unique features. These include self-assembly or the ability to make use of the enhanced permeability and retention capacity that most malignancies have as a consequence of leaky neoangiogenesis and the absence of a functional lymphatic system.[149] Nanostructures (Table 2) can also be designed to carry useful payloads that include low molecular weight chemotherapy agents or contrast agents.[150,151] Moreover, the newly formed structures are able to rapidly detect cancer cells, load multiple anticancer agents on their surface, and deliver the drugs rapidly at the target cell,[152–154] while preventing their bioactive cargo degradation when the investigator chooses to use an RNA-based approach.

Non-Hodgkin's lymphomas are the most common lymphohematopoietic malignancies both in the US and in Europe.[166] One particular type is anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma, which is a very aggressive T-cell lymphoma with an abnormal expression of both the *ALK* oncogene, as well as the surface protein, CD30.[167–169] A nucleic acid-based knockdown of *ALK* gene expression has been proven to promote cell death of the malignant T-cell.[170,171] Mori et al[172] have developed an RNA aptamer that specifically binds to the CD30 epitope. Zhao et al[173] have subsequently hypothesized that a lymphoma cell-selective delivery of a tumor gene-specific siRNA could be achieved by assembling a functional RNA nanocomplex comprising the CD30-specific aptamer and the ALK-targeted siRNA, all within a nanosized PEG-based polymer carrier. PEG-based structures are considered to be rather safe, as toxicity assays done using BALB/c mice showed little or no side effects, except for 40% accumulation in the liver.[174] This new approach proved that the nanocomplex could be cancer cell-selective and cancer gene-specific, with great potential in the clinic if hepatic damage can be avoided.

Another non-Hodgkin's lymphoma with a very aggressive behavior and short-term survival is mantle cell lymphoma. This particular type of malignancy is resistant to most therapeutic approaches, including immunochemotherapy and stem cell transplantation, leading investigators to look for different salvage treatment options.[175–178] SYK is a new target for the management of B-lineage leukemias and lymphomas,[179] as it regulates apoptosis by controlling activation of the phosphoinositide 3-kinase/AKT, nuclear factor-kappa B, and signal transducer and activator of transcription 3 pathways, which are all very important in the signaling of the stem cell lineage.[180,181] Cely et al[182] reported a different approach by developing a nanotechnology-based platform that can be used to target a very selective SYK inhibitor for the lymphoma cell. The designed liposomal nanoparticle was the pentapeptide mimic, 1,4-bis(9-O-dihydroquinidinyl)phthalazine/hydroquinidine 1,4-phathalazinediyl diether (C16). The liposomal nanoparticle of C16 was shown to induce apoptosis of the lymphoma cell after 24 hours, providing the scientific background for an alternative treatment for refractory mantle cell lymphoma.[182] However, previous experience using liposomes shows that this treatment strategy is accompanied by several side effects. For patients with AIDS-related Kaposi's sarcoma, 30% of those treated with Doxil presented with low blood counts and palmar–plantar erythrodysesthesia,[183,184] yet the clinicians easily managed these symptoms.

Carbon nanotubes are tubes made out of graphic carbon that have very good mechanical strength, good flexibility, and excellent thermal and electrical conductivity,[185–187] qualities that initially made them suitable candidates for novel drug design. These tubes have been conjugated with monoclonal antibodies and plasmid deoxyribonucleic acid (DNA) in order to achieve cancer cell inhibition,[188–191] and conjugates have also been made with paclitaxel and other cytostatics.[192] Liu et al inhibited the growth of breast cancer by conjugating carbon nanotubes with paclitaxel, and they showed that the intravenous administration of 10 mg/kg of the new com-

Table 2 Various nanostructures used in translational cancer research

Disease	Nanostructure	Active agent	Biological effect	Reference
Kaposi sarcoma	Liposomes	Doxorubicin	Cytostatic	155
Colorectal cancer	Carbon nanotubes	Anti-EGFR antibody	Cytostatic	156
Melanoma	Carbon nanotubes	Hematoporphyrin monomethyl ether	Photodynamic therapy	157
Malignant gliomas	Carbon nanotubes	Tumor lysate	Vaccination	158
Breast cancer	Carbon nanotubes	Paclitaxel	Cytostatic	159
Pancreatic cancer	Gold nanoparticles	Bortezomib	Cytostatic	160
Breast cancer	Gold nanoparticles	Gadolinium chelate	Diagnostics	161
Neuroblastoma	Gold nanoparticles	Barium titanate	Photothermal therapy	162
Hepatocellular carcinoma	Silver nanoparticles	Protein conjugate silver sulfide	Cytostatic	163
Breast cancer	Quantum dots	Mortalin antibody	Diagnostics	164
Lung cancer	Quantum dots	$CdTE:Zn^{2+}$	Diagnostics	165

Abbreviation: EGFR, epidermal growth factor receptor.

pound enhanced the therapeutic efficacy when compared with doxorubicin-free treated mice.[104] Still, because of their fiber shape and size, carbon nanotubes cause cytotoxicity, inflammation, and DNA damage in vitro.[193–196] The animal models used to study the toxic effects of carbon nanotubes demonstrated that the high concentrations needed to induce the regression of the tumor may cause chronic lung inflammation, foreign-body granulomas, or interstitial fibrosis,[197–200] limiting their potential clinical use.

Other types of nanoparticles with biomedical application are metallic colloidal gold and silver.[201–206] These structures are used for photothermal ablation therapy, as well as for contrast enhancers in computed tomography or X-ray diagnostics.[207,208] Niidome et al[202] have reported no toxicity in their studies in a mouse model of colon adenocarcinoma after having used intravenous PEG-coated nanorods, in spite of the fact that gold may interact with intracellular proteins and modify their structure, causing autoimmune-related toxicity. Silver nanostructures are commercially available for antimicrobial use,[209,210] yet recent data show that silver oxide may also be used in cancer research, as the nanostructure cargo can induce the regression of cancer neoangiogenesis.[211–214] Still, toxicity limits their use because silver nanoparticles can cause destruction of the blood–brain barrier, brain degeneration, and edema,[215–217] as well as liver failure.[218]

Diagnostics can also be aided based on diffident nanostructures types including quantum dots or metallic core-shell nanoparticles that usually contain cadmium telluride, cadmium selenide, and either indium arsenide or indium phosphide.[1,2] This structure is then covered by a shell of zinc sulfide and is subsequently coated with PEG in order to facilitate the attachment of various drugs, nucleic acids, or antibodies.[219–221] These structures are very good fluorophores because of their broad-spectrum fluorescence,[222] and they can be used to properly identify cancer cells, as well as signal events such as peroxisome activity or the presence of certain membrane receptors.[223–226] Toxicity in clinical use is not known in great detail, but it seems that following the removal of the coating after their exposure to oxidative environments such as the endosome,[227–229] quantum dots may be very toxic, which may limit their clinical use (Figure 3).

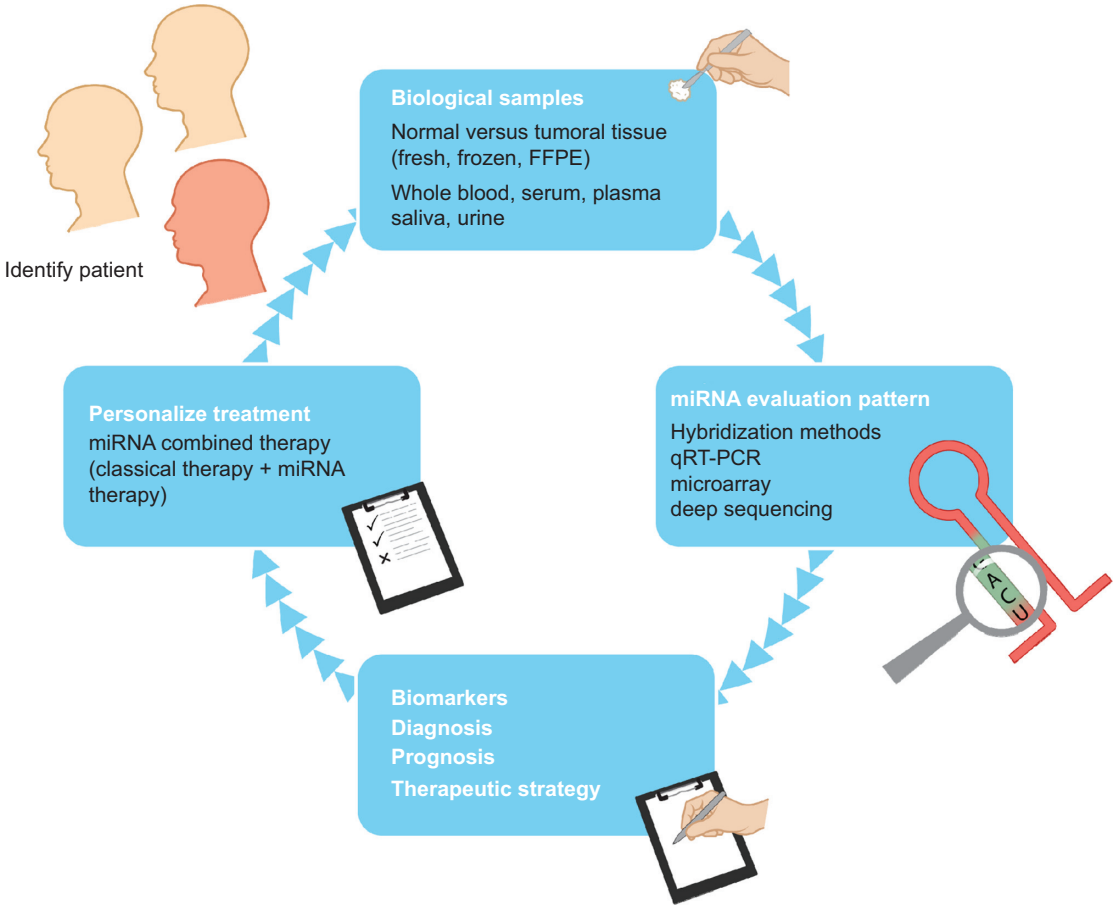

Figure 3 Bench-to-bedside evolution in translational hematology and oncology.
Abbreviations: FFPE, formalin-fixed, paraffin-embedded; miRNA, micro ribonucleic acid; qRT-PCR, quantitative real-time polymerase chain reaction.

Conclusion

In recent years, important progress has been made in nanotechnology, with its ever-increasing applicability in basic and translational medicine, leading to the appearance of a new field known as nanomedicine. This new science deals with the engineering of various structures of nanoscale dimensions that can be properly conjugated with various highly specific targeting agents in order to be used in the clinic, for either early diagnostic purposes or for disease treatment.[1,2]

These endeavors are possible because nanoparticles have unique properties, such as a preferential accumulation in the neoplastic tissue in comparison with healthy cells.[1,2] These particles hold great potential for possibly replacing current active agents, which have been shown to be highly inefficient, based on epigenetics and molecular pharmacology principles. This step in clinical oncology and hematology is, however, still far from being implemented in clinical practice. Nevertheless, with each experimental report, we come closer to a patient-tailored approach in order to achieve maximum anticancer effects with minimal side effects.

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Disclosure

The authors report no conflicts of interest in this work.

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