

Tumor-Targeted & Tumor Microenvironment-Responsive Nanoparticles in Cancer and Chronic Disease Therapy

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Abstract:

Nanotechnology has become an outstanding approach to the contemporary therapeutics especially to cancer and chronic diseases in which the traditional drug delivery systems have limitations including lack of specificity, systemic toxicity, and insufficient bioavailability. The pathological conditions of acidic pH, hypoxia, redox imbalance, and overexpressed enzymes can be used as the site-specific delivery of the drug and the controlled release of nanoparticles, which is why the use of tumor-targeted and tumor microenvironment-responsive nanoparticles is a promising solution. These intelligent nanocarriers enhance the therapeutic outcomes with a reduction in adverse effects. Outside of oncology, other chronic diseases such as diabetes, cardiovascular diseases, inflammatory diseases and neurodegenerative diseases are also investigating the use of such nanoparticles. In this review, the author thoroughly addresses the concepts of tumor targeting, the tumor microenvironment, responsive nanoparticles, their use in cancer and chronic disease therapy, current developments, and issues, as well as future insights.

Keywords: Tumor targeting, Tumor microenvironment, Responsive nanoparticles, Cancer therapy, Chronic diseases, Smart drug delivery

1. Introduction

The cancer and chronic diseases still present some of the most severe health issues all over the world, with a significant share of morbidity, mortality, and healthcare spending on them. In spite of the ongoing progress in the field of pharmacotherapy and biomedical research, the successful treatment of these diseases is still restricted by various inherent limitations of the traditional drug delivery systems. The conventional therapeutic methods are usually not specific and so there will be non-selective dispensing of drugs resulting in systemic toxicity, frequent dosing schedules, and lack of compliance among patients. These restrictions have compelled the quest of new approaches that can enhance the effectiveness of the therapeutic efficacy and reduce the side effects. Here, the drug delivery system through nanotechnology has become a groundbreaking technology in the contemporary medicine.

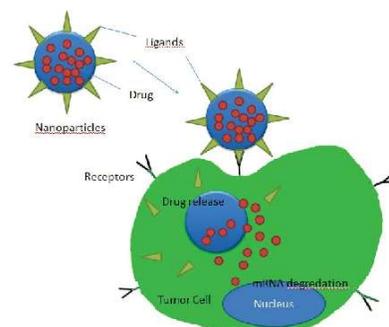


Figure 1

nanotechnology
medicine.

In the last two decades, nanomedicine has demonstrated a great potential to enhance the solubility, stability, bioavailability, and pharmacokinetic of a large variety of drugs. More to the point, nanoparticles can be designed

to target diseased locations with selective accumulation, and spill its cargo in reaction to particular biological cues. Tumor-targeted and tumor microenvironment-responsive nanoparticles are among the many techniques of nanotechnology that have received much interest because of their potential in addressing the complicated pathology of cancer and chronic diseases.

Although they show a great potential, the clinical application of tumor-targeted and microenvironment-responsive nanoparticles is associated with a number of challenges. There should be a careful consideration of the problems of large-scale manufacturing, reproducibility, long-term safety, regulatory approval and inter-patient variability in tumor biology. However, ongoing advancements in the fields of materials science, biotechnology and pharmaceutical engineering are hastening the process of developing clinically viable products of nanomedicine.

2. Tumor Targeting Strategies

The fundamental concept in the nanoparticle-based drug delivery system is tumor targeting, which focuses on selective delivery of therapeutic agents to cancerous tissues with minimum harm of normal cells. Standard anticancer agents diffuse all over the body result in non-selective uptake and systemic toxicity. However, tumor targeting strategies are implemented to advance these weaknesses by maximizing drug concentration in the tumor locations and therapeutic efficacy. Generally, there are two categories of tumor targeting namely passive targeting and active targeting, which have complementary roles in contemporary nanomedicine.

2.1 Passive Targeting

Passive targeting mode is mainly on the Enhanced Permeability and Retention (EPR) effect which is a phenomenon that is evident in most solid tumors. The abnormality of tumor tissues is the leaky blood vessels caused by rapid and uncontrolled angiogenesis. These are blood vessels with big endothelial gaps, which enable the extravasation of nanoparticles with the right size to the tumor tissues with ease. Also, the tumors do not have a good lymphatic drainage system thus causing the nanoparticles to stay longer at the tumor site. Passive targeting nanoparticles are usually of the size between 10-200 nanometers and thus they are capable of circulating longer and concentrating in tumor tissues. Passive targeting does not involve surface modification by use of any special ligand, thus is relatively easier and inexpensive. This approach has been prolific in various clinically approved nanomedicine preparations. Passive targeting however is very variable and its success is based on the type of tumor, location, vascularization and the difference

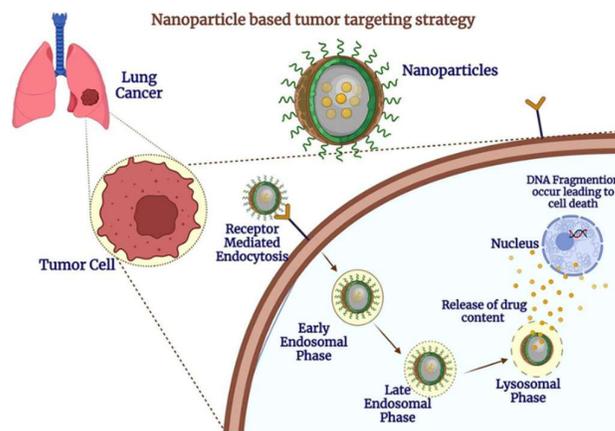


Figure 2

in the individual patients. Nanoparticle accumulation in some types of tumors is poor because of their poor EPR effects. Also, passive targeting might not guarantee effective uptake by cancer cells upon reaching the cancer tissue by nanoparticles. Passive targeting, thus, is a means of offering a basis in targeting, but it is usually used alongside active targeting measures to improve therapeutic effects.

2.2 Active Targeting

Active targeting entails the functionalization of nanoparticles surfaces using certain ligands capable of identifying and affinity to specific receptors that are overexpressed on cancer cells or tumor related tissues. These ligands are antibodies, peptides, aptamers, sugars, vitamins and small molecules. When nanoparticles bind to target receptors, receptor-mediated endocytosis takes place leading to increased intracellular delivery of the drug into the cancer cells. Receptors that

are commonly used in cancer therapy are: folate receptors, transferrin receptors, epidermal growth factor receptors, and human epidermal growth factor receptor

2. Active targeting,

through the exploitation of these molecular differences between cancerous and normal cells means that selectivity and therapeutic precision is greatly enhanced. Active targeting is also useful in overcoming multidrug resistance by raising the intracellular disease concentration and circumventing efflux mechanisms. **2.3 Dual and Multistage Targeting Strategies.**

Modern nanomedicine increasingly uses active and passive targeting mechanisms together to achieve the maximum therapeutic effect, through the application of dual or multistage targeting. Under these systems, the nanoparticles are initially concentrated in the tumor site under EPR effect and then by active targeting ligands on the specific receptors of the cancer cells. The sequential targeting improves localization of the tumor, as well as the uptake of the cell.

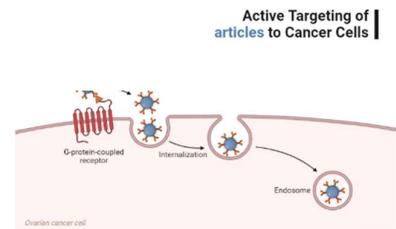


Figure 3

3: Tumor Microenvironment

Contrary to the normal tissue setting, the tumor microenvironment is an altered micro-environment with abnormal physicochemical and biological conditions that are relevant in tumor initiation, progression, metastasis as well as being resistant to therapy. The tumor microenvironment has been a fundamental concept in the recent years in the creation of sophisticated drug delivery systems, especially tumor-targeted and microenvironment-sensitive nanoparticles.

The tumor microenvironment includes malignant cells, stromal cells (fibroblasts and endothelial cells), immune cells, elements of extracellular matrix, and blood vessels. These parts are interacting in a continuous manner in terms of biochemical and mechanical signals. These interactions do not only promote tumor growth but also form obstacles which reduce the efficacies of the traditional treatment. This has made tumor microenvironment as a significant therapy target in addition to the cancer cells. Abnormal tumor vasculature is one of the most unique characteristics of the tumor microenvironment. Uncontrolled and very fast angiogenesis results in irregular, leaky and poorly organized blood vessels. The vessels are causing uneven blood flow, restriction of oxygen supply, and an ineffective delivery of drugs. Even though this disrupted vasculature helps nanoparticles to become more permeable, it causes hypoxic areas that undermine the efficacy of chemotherapy and radiotherapy. Another characteristic of the tumor microenvironment is acidic PH. Cancer cells have a high metabolic rate and depend on glycolysis, which produces a lot of lactic acid, resulting in the decrease of extracellular pH to a lower level than in the normal tissues. This acidic condition facilitates tumor invasion, inhibits immune reactions and causes drug resistance. Acidic pH can

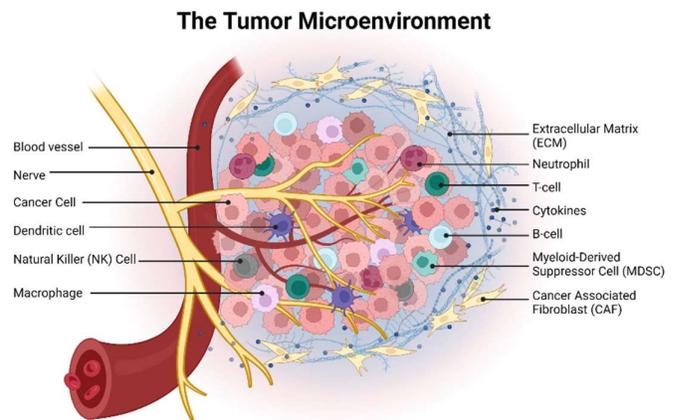


Figure 4

also be used as a good stimulus to pH-responsive nanoparticles, in both terms, drug release is selective in tumor tissues and remains stable at normal physiology conditions.

The microenvironment in the tumor is also abundant in tumor-associated enzymes, including matrix metalloproteinases and cathepsins. Such enzymes are essential in the degradation of the extra-cellular matrix, tumor invasion and metastasis. The expression of these enzymes is another stimulus mechanism of enzyme-responsive nanoparticles which enable site-specific activation of drugs to achieve site-specific therapeutic selectivity. The tumor microenvironment also suppresses the immune system, which complicates the treatment of cancer even more. The tumors do tend to attract immunosuppressive cells and release inhibitory cytokines so that they can evade immune surveillance. Such immunosuppressive environment restricts the efficacy of immunotherapies but can also be considered a viable target of nanoparticle-based delivery of immunomodulatory agents. One of the greatest challenges associated with cancer treatment is the heterogeneity of the tumor microenvironment. There are differences in the PH, oxygen levels, enzymes expression and not only between the different types of the tumor but also between the different sections of the tumor in question. This complexity requires a creation of multifunctional nanoparticle systems that can respond to several stimuli at the same time.

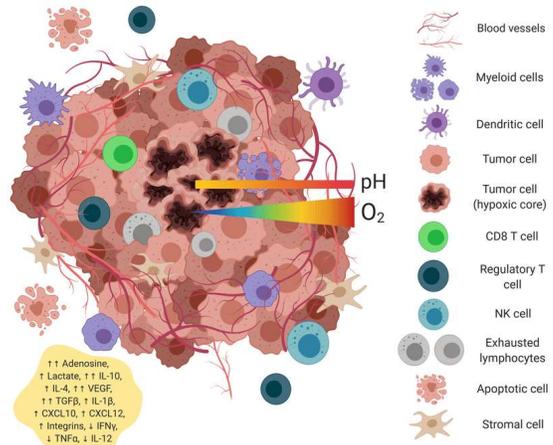


Figure 5

the composition of the cell

4. Tumor Microenvironment-Responsive Nanoparticles

Tumor microenvironment-reactive nanoparticles constitute an enhanced group of smart drug delivery systems that respond selectively to the deviant physicochemical settings that are found within tumor tissues. These systems are programmed to detect certain stimuli in the tumor microenvironment and release drugs at the appropriate point as compared to conventional nanoparticles that only depend on passive or active targeting.

The microenvironment of the tumor is significantly different (compared to normal tissues) with regard to the pH, oxygen concentration, redox potential, enzyme expression, and metabolic activity. Using such disparities, nanoparticles that are sensitive to microenvironment are able to gain spatiotemporal control over drug delivery. These kinds of smart systems stay at a steady state even during circulation but become triggered when they undergo tumor-specific conditions, thus enhancing the effectiveness and safety of treatment.

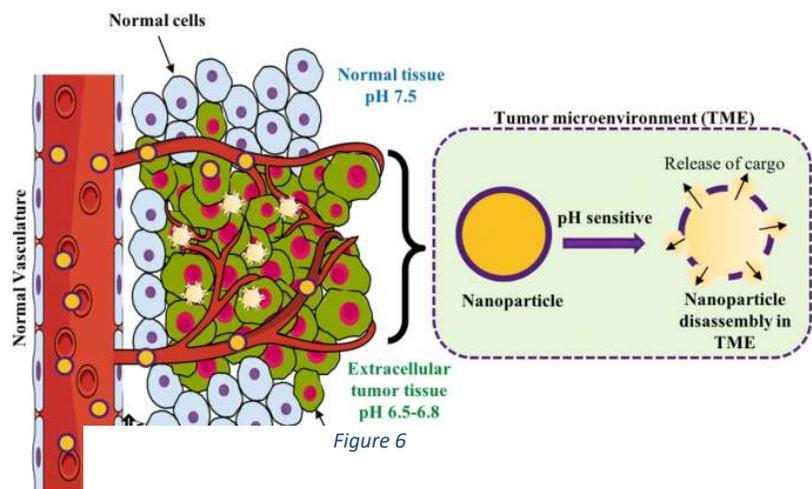


Figure 6

4.1 Nanoparticles that Respond to pH.

pH-responsive nanoparticles have been studied as one of the most widely researched microenvironment-responsive systems. The acidic environment of tumor tissues and intracellular compartments, including endosomes and lysosomes, is more acidic than the physiological conditions and, according to this criterion, pH-responsive nanoparticles are produced with the help of acid-sensitive polymers, linkers, or coatings, which change structure or degrade at acidic pH. Consequently, the encapsulated drug is discharged selectively in tumor tissues or within cancer cells.

4.2 Nanoparticles Responsive to Redox.

Nanoparticles that respond to redox utilize the redox imbalance of cancer cells. Glutathione level in the tumor cells is usually high as compared to normal cells. Redox-responsive systems make use of redox-sensitive bonds, like disulfide bonds, which are stable in the extracellular environment, but cleave in the presence of high intracellular glutathione amounts. When absorbed by the cancer cells, these nanoparticles easily release their drug cargo, making the intracellular drug concentration achieve high levels. Nanoparticles that are redox-responsive come in especially handy to deliver chemotherapeutic agents, genes and proteins because intracellular delivery can be enhanced at minimum off-target toxicity.

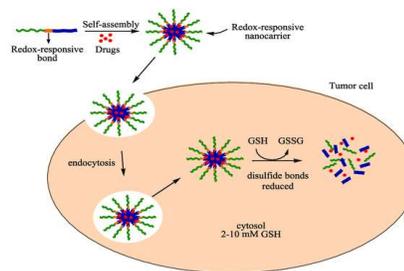


Figure 7

4.3 Nanoparticles Responsive to Enzymes.

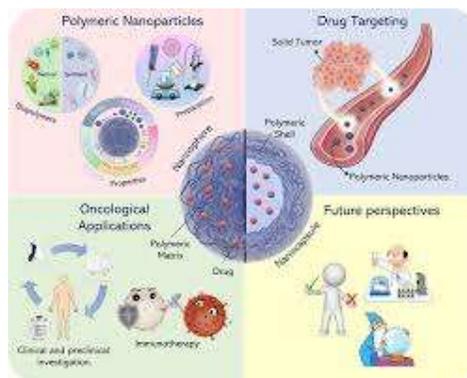
The rapid tumor growth and remodelling of the extra cellular matrix result in the overexpression of certain enzymes in tumour tissues. Nanoparticles that are responsive to enzymes are engineered to respond to these tumor-associated enzymes. After interacting with these enzymes, the nanoparticle structure disintegrates or transforms in conformation leading to drug release. The strategy is highly specific since drugs are only released when there are target enzymes. Nanoparticles that can be responsive to enzymes are particularly promising in the case of invasive and metastatic tumors, in which there is high enzymatic activity. Hypoxia-responsive nanoparticles are synthetic particles that react to changes in oxygen levels within the body, typically due to the physiological state of stress or injury (Cock 116).<|human|>4.4 Hypoxia-Responsive Nanoparticles Hypoxia-responsive nanoparticles are artificial particles responsive to the presence or absence of oxygen in the body, usually in the physiological stress or injury state (Cock 116).

5. Types of Nanoparticles Used

1. Polymeric Nanoparticles

Polymeric nanoparticles are prepared using biodegradable and biocompatible polymers such as PLGA, chitosan, and polyethylene glycol. They allow controlled and sustained drug release and can be easily modified for tumor targeting and microenvironment responsiveness.

2. Lipid-Based Nanoparticles



This category includes liposomes, solid lipid nanoparticles, and nanostructured lipid carriers. They exhibit excellent biocompatibility, high drug encapsulation efficiency, and are widely used in cancer and chronic disease therapy. *Figure 8*

3. Dendrimers

Dendrimers are highly branched macromolecules with a well-defined structure. They offer high drug loading capacity and precise surface functionalization for targeted and stimuli-responsive drug delivery.

4. Inorganic Nanoparticles

Inorganic nanoparticles such as gold, silica, iron oxide, and quantum dots possess unique optical and magnetic properties. They are commonly used for targeted therapy, imaging, and theranostic applications.

5. Hybrid Nanoparticles

Hybrid nanoparticles combine organic and inorganic materials or polymer–lipid systems. They integrate multiple functionalities, including **targeting, controlled release, and diagnostic capability.**

6. Cancer Therapy Applications.

Nanoparticles that are tumor-targeted and tumor microenvironment-responsive have become strong platforms to use in cancer treatment in that they eliminate the key weaknesses of standard methods of treatment. The conventional methods of cancer treatment including chemotherapy, radiotherapy as well as surgery usually experience non-specific distribution of drugs, dose limiting side effects, and development of drug resistance. Nanoparticle-based systems provide a better and more accurate method by increasing drug concentration at the tumor sites, cellular uptake as well as controlled drug release.

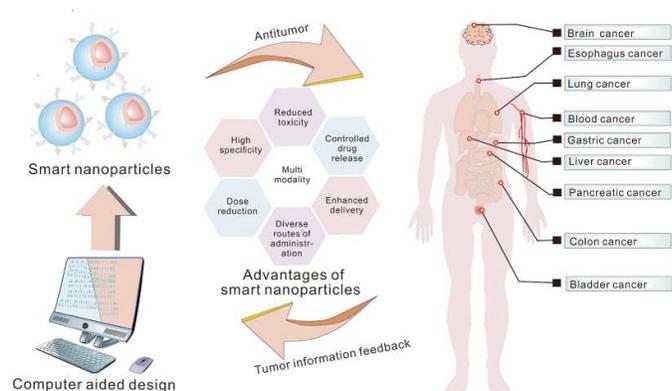
6.1 Targeted Chemotherapy

Targeted chemotherapy is one of the major uses of nanoparticles in cancer therapy. The chemotherapeutic agents tend to be lack of selectivity resulting in severe side effects in normal

tissues. Nanoparticles that target tumors enhance the therapeutic index of these drugs because they passively and actively target tumor tissues.

6.2 Multidrug Resistance

Resistance to many drugs has become a significant problem for healthcare practitioners in developing nations. The issue of multidrug resistance is a paramount concern in treating cancer since it is commonly linked to efflux pumps, altered drug metabolism, and tumor heterogeneity. Nanoparticles are useful because they overcome multidrug resistance by increasing the intracellular concentration of drugs and circumventing efflux. Redox and enzyme-responsive nanoparticles guarantee a quick release of drugs into the cancer cells and enhance treatment up to the resistance of the tumors. *Figure 9*



6.3 Gene Therapy and Delivery of Nucleic Acids.

Nanoparticles are important in the process of cancer gene therapy in that they aid the delivery of nucleic acids like siRNA, miRNA, and plasmid DNA. These therapeutic agents are very vulnerable to enzymes degradation and have low cellular uptake with a single administration. Nanoparticle carriers ensure that genetic material is not degraded and that it enters the tumor cell. Microenvironment-based system systems also promote the silencing of genes or the activation of genes in the tumor tissues with high efficacy, which will also boost therapeutic responses.

6.4 Photodynamic Therapy/ Photothermal Therapy.

Nanoparticles in photothermal therapy process light energy into heat which destroys local tumor cells. In photodynamic therapy nanoparticles transport photosensitizers that are active when activated by light to form reactive oxygen species, which induce the death of cancer cells. Tumor-targeted nanoparticles improve the delivery of photothermal agents and photosensitizers in-vitro in the tumor site, improving accuracy in treatment and reducing the adverse effects on the surrounding normal tissues.

6.5 Cancer Immunotherapy Immunotherapy of cancer

using nanoparticle-based systems is being used more often to control the immune response to tumors. Immunomodulatory reagents, antigens or adjuvants can be delivered directly to immune cells or tumor tissues by nanoparticles. Nanosensors responsive to tumor microenvironment aid in counteracting immunosuppressive tumor microenvironment and boosts immune activation and tumor immunotherapeutic efficacy.

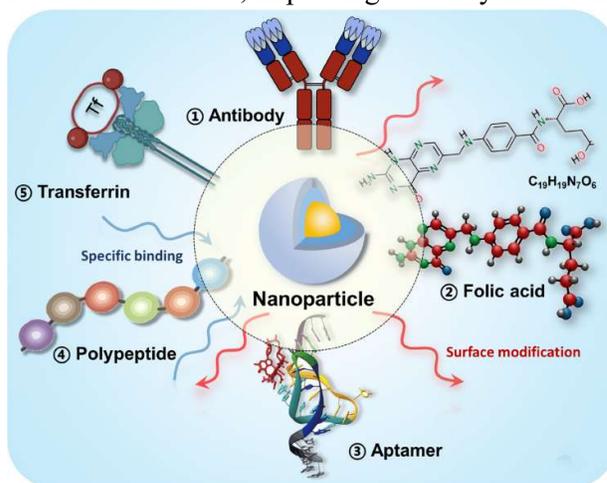


Figure 10

6.6 Combination Therapy

Nanoparticles can facilitate simultaneous delivery of a variety of therapeutic agents, chemotherapeutic drugs and gene therapy agents, into a single particle. This method enables synergistic treatment programs that are able to address several cancer pathways in tandem. Nanoparticles that are microenvironmental responsive meet their sequential release or controlled release requirements to enhance the efficacy of the treatment and minimize adverse effects.

6.7 Clinical Cancer Management Advantages.

Some of the clinical advantages of tumor-targeted responsive nanoparticles in cancer treatment are: better bioavailability of drugs, there is low administration frequency, patient compliance, and low toxicity to the system. Such systems are also capable of individualized treatment interventions through the customization of drug delivery to tumor attributes.

Conclusion

Tumor-directed and tumor microenvironmental-reactive nanoparticles can be seen as a significant breakthrough in the sphere of contemporary drug delivery and precision medicine. The traditional treatment methods of cancer and chronic illnesses have been restricted in most cases due to non-specificity in drug delivery, systemic toxicity, lack of bioavailability and occurrence of drug resistance. Incorporation of nanotechnology in therapeutic

approaches has offered new solutions to these problems since nanotechnology has enabled the use of controlled, site-specific, and stimulus-responsive drug delivery. Tumor targeting approaches, such as passive and active targeting have enhanced the selective concentration of therapeutic agents at the tumors sites tremendously. Passive targeting uses the special vascular properties of tumors and active targeting improves cellular absorption by ligand-receptor interactions. These strategies in combination with tumor microenvironment-responsive mechanisms enable the selective delivery of nanoparticles drug cargo to pathological conditions in acidic pH, hypoxia, redox imbalance, and enzyme overexpression. This smart reactivity limits premature release of drugs, as well as, damages to healthy tissue, hence enhancing the therapeutic index. The microenvironment associated with tumor is critical to the development of the disease, its metastasis, and resistance to therapy. Tumor microenvironment Researchers have changed the tumor microenvironment into a therapeutic target by creating nanoparticles that respond to microenvironmental stimuli, and therefore, nanoparticles that respond to pH, redox, enzyme, and hypoxia have been shown to be more effective in delivering chemotherapeutic agents, genes, and immunomodulators. Such systems have the advantage of not only enhancing success with anticancer therapy but also combating one of the greatest challenges in treating cancer, i.e. multidrug resistance. In addition to in the cancer field, tumor-targeted and microenvironment-responsive nanomedicine have demonstrated very high potential in chronic disease treatment. The pathological characteristics of conditions like diabetes, cardiovascular disorders, inflammatory diseases, and neurodegenerative disorders are similar and include aspects such as oxidative stress, inflammation, and abnormal enzyme activity. Delivery systems of nanoparticles are used to facilitate sustained and regulated drug release, localization to a specific tissue and improved compliance by patients in long-term therapy.

Although these advanced nanomedicine systems have remarkable potential, there are a number of challenges in the clinical translation of these systems. The aspect of large-scale manufacturing, reproducibility, safety in the long term, regulatory registration, and inter-patient variation have to be taken into consideration thoroughly. Further, heterogeneity and complexity of tumors and chronic diseases require building of multifunctional and adaptable nanoparticle platforms. These barriers can be overcome through further interdisciplinary studies in fields of pharmaceutical sciences, materials engineering, biotechnology, and clinical medicine.

References

1. Peer D, et al. Nanocarriers as an emerging platform for cancer therapy. *Nat Nanotechnol.* 2007;2:751–760.
2. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect. *J Control Release.* 2000;65:271–284.
3. Torchilin VP. Multifunctional nanocarriers. *Nat Rev Drug Discov.* 2014;13:813–827.
4. Allen TM, Cullis PR. Liposomal drug delivery systems. *Adv Drug Deliv Rev.* 2013;65:36–48.
5. Duncan R. Polymer conjugates as anticancer nanomedicines. *Nat Rev Cancer.* 2006;6:688–701.
6. Danhier F, et al. Targeting cancer with nanoparticles. *J Control Release.* 2010;148:135–146.
7. Jain RK. Normalization of tumor vasculature. *Science.* 2005;307:58–62.

8. Minchinton AI, Tannock IF. Drug penetration in solid tumors. *Nat Rev Cancer*. 2006;6:583–592.
9. Fang J, Nakamura H, Maeda H. EPR effect in macromolecular therapeutics. *Adv Drug Deliv Rev*. 2011;63:136–151.
10. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design. *Nat Biotechnol*. 2015;33:941–951.
11. Chauhan VP, Jain RK. Strategies for advancing cancer nanomedicine. *Nat Mater*. 2013;12:958–962.
12. Greish K. Enhanced permeability and retention effect. *Methods Mol Biol*. 2010;624:25–37.
13. Lammers T, et al. Nanomedicine in cancer therapy. *Nat Rev Clin Oncol*. 2012;9:460–475.
14. Sun Q, et al. Smart nanoparticles in cancer therapy. *Adv Drug Deliv Rev*. 2017;115:1–24.
15. Yu J, et al. pH-responsive nanoparticles. *Acta Pharm Sin B*. 2018;8:34–48.
16. Bae YH, Park K. Targeted drug delivery to tumors. *J Control Release*. 2011;153:198–205.
17. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers. *Nat Mater*. 2013;12:991–1003.
18. Chen H, et al. Redox-responsive nanocarriers. *Adv Drug Deliv Rev*. 2018;135:68–86.
19. Torchilin VP. Targeted pharmaceutical nanocarriers. *Pharm Res*. 2007;24:1–16.
20. Zhang X, et al. Enzyme-responsive drug delivery systems. *Chem Rev*. 2018;118:337–383.
21. Lu Y, Low PS. Folate-mediated targeting. *Adv Drug Deliv Rev*. 2012;64:342–352.
22. Ferrari M. Cancer nanotechnology. *Nat Rev Cancer*. 2005;5:161–171.
23. Huang X, et al. Gold nanoparticles in cancer therapy. *Adv Drug Deliv Rev*. 2011;63:132–142.
24. Jain S, et al. Polymeric nanoparticles in drug delivery. *Crit Rev Ther Drug Carrier Syst*. 2010;27:1–43.
25. Kesharwani P, Jain K, Jain NK. Dendrimers as nanocarriers. *Prog Polym Sci*. 2014;39:268–307.
26. Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics. *Nat Rev Drug Discov*. 2008;7:771–782.
27. Peer D. Tumor-targeted nanocarriers. *Curr Opin Biotechnol*. 2010;21:605–611.
28. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. *Annu Rev Med*. 2012;63:185–198.
29. Shi J, et al. Nanotechnology in drug delivery. *Nat Rev Drug Discov*. 2017;16:701–715.
30. Yang G, et al. Hypoxia-responsive nanomedicine. *Adv Mater*. 2019;31:1901513.
31. Liu Y, et al. Tumor microenvironment-responsive nanocarriers. *Adv Funct Mater*. 2020;30:1908884.
32. Zhang Y, et al. Smart drug delivery systems. *Biomaterials*. 2019;197:61–75.
33. Raza F, et al. Recent advances in nanomedicine. *J Control Release*. 2019;314:13–28.
34. Senapati S, et al. Controlled drug delivery systems. *Adv Drug Deliv Rev*. 2018;136–137:1–18.
35. Shi Y, et al. Nanotechnology in cancer treatment. *Adv Mater*. 2020;32:1904393.
36. He C, Lu K, Liu D, Lin W. Nanoscale metal–organic frameworks. *J Am Chem Soc*. 2014;136:5181–5184.
37. Zhang L, et al. Lipid-based nanoparticles. *Adv Drug Deliv Rev*. 2012;64:140–153.

38. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable nanocarriers. *Chem Rev.* 2016;116:2602–2663.
39. Chauhan VP, Stylianopoulos T. Tumor microenvironment barriers. *Nat Rev Clin Oncol.* 2014;11:273–284.
40. Kwon GS. Polymeric micelles for drug delivery. *Crit Rev Ther Drug Carrier Syst.* 2003;20:357–403.
41. Bobo D, et al. Nanoparticle-based medicines. *Pharm Res.* 2016;33:2373–2387.
42. Wicki A, et al. Nanomedicine in cancer therapy. *J Control Release.* 2015;200:138–157.
43. Moghimi SM, Hunter AC, Murray JC. Nanomedicine challenges. *Pharmacol Rev.* 2001;53:283–318.
44. Wilhelm S, et al. Analysis of nanoparticle delivery. *Nat Rev Mater.* 2016;1:16014.
45. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine. *Nat Rev Cancer.* 2017;17:20–37.
46. Liu D, et al. Stimuli-responsive drug delivery. *Adv Funct Mater.* 2019;29:1806194.
47. Torchilin VP. Recent advances in nanocarriers. *Adv Drug Deliv Rev.* 2011;63:131–135.
48. Peer D, Margalit R. Tumor targeting by nanoparticles. *Int J Cancer.* 2004;108:780–789.
49. Wang S, et al. Nanoparticles in chronic disease therapy. *Drug Discov Today.* 2019;24:2037–2045.
50. Liu Z, et al. Nanomedicine in inflammation. *Adv Drug Deliv Rev.* 2020;160:114–138.
51. Poon W, et al. Nanoparticle delivery challenges. *Trends Biotechnol.* 2020;38:950–962.
52. Chen Y, et al. Nanoparticles in immunotherapy. *Adv Mater.* 2021;33:2007714.
53. Zhang H, et al. Targeted nanomedicine. *ACS Nano.* 2020;14:12320–12340.
54. Mura S, Couvreur P. Nanotheranostics. *Adv Drug Deliv Rev.* 2012;64:1394–1416.
55. He Q, Shi J. Mesoporous silica nanoparticles. *Adv Mater.* 2014;26:391–411.
56. Yang X, et al. Multifunctional nanomedicine. *Biomaterials.* 2020;232:119739.
57. Rwei AY, et al. Nanoparticles in pain and chronic disease. *Nat Rev Mater.* 2015;1:16024.
58. Li Y, et al. Nanotechnology-based drug delivery. *J Pharm Sci.* 2018;107:2143–2156.
59. Kim BYS, Rutka JT, Chan WCW. Nanomedicine. *N Engl J Med.* 2010;363:2434–2443.
60. Farokhzad OC, Langer R. Impact of nanotechnology. *ACS Nano.* 2009;3:16–20.