Challenges in Development of Nanomedicine for Treatment of Cancer

Dimple Sethi Chopra*

Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, India

Abstract: The inherent limitations of conventional cancer therapies have stimulated the growth of cancer nanomedicine. This is primarily attributable to its unique features for drug delivery, diagnosis and imaging, synthetic vaccine development and miniature medical devices, supplemented with the inherent therapeutic property of some nanomaterials. Nanotherapies that integrate some of these features are already in use and others have great potential in clinical development, with definitive results in near future. In order to develop smart cancer nanomedicine, it is very essential to bridge the gap between Bio-Nanoscience and Cancer Nanomedicine with a better understanding about the molecular basis of cancer. The development of smart cancer nanomedicine can be accelerated by patient stratification, rational drug selection, combination therapy, synergism with immunotherapeutics. The nanoplatforms that exhibit a significant increase in progression free survival are most desirable.

Keywords: Nanomaterials, Smart Cancer Nanomedicine, tumors, heterogeneity, overall survival, immunotherapeutics.

1. INTRODUCTION

Since the beginning of era of cancer chemotherapy in 1940s, there has been significant improvement in anticancer drugs resulting in treatment for many fatal cancers. The adjuvant chemotherapy and hormonal therapy have been found to improve overall survival and prevent disease recurrence following surgical resection of malignancies. Despite increased number of therapeutic options, the cancer therapy remains a challenge for physicians and researchers because of tumour resistance. In this context, a better understanding about the molecular basis of cancer is utmost important for development of therapeutic strategies that allow an effective combat against this malignancy and improve quality of life for patients. The inherent limitations of conventional cancer therapies prompted the development and application of various nanotechnologies for more effective and safer cancer treatment, referred to as cancer nanomedicine. Abraxane is one of the nanotechnology-based drugs that has been approved by the U.S. Food and Drug Administration (FDA) to treat breast cancer, non-small-cell lung cancer (NSCLC) and pancreatic cancer. It is commercially available. It is paclitaxel containing albumin nanoparticles [1].

The growing interest in applying nanotechnology to cancer is principally attributed to its uniquely appealing features for imaging and diagnosis, drug delivery, synthetic vaccine and miniature medical devices development. This also include nanomaterials having inherent therapeutic properties. Nanotherapies that incorporate some of these features (for example, improved circulation and reduced toxicity) are already in use today, and others show great promise in clinical development, with definitive results expected in the near future.

Presently available nanotherapies exhibit improved mean residence time and reduced toxicity and many of them under clinical evaluation have immense potential in near future. Nanoplatforms like liposomes, albumin nanoparticles, polymeric micelles have been approved for cancer treatment whereas, hyperthermia, immunotherapy, radiation therapy, gene or RNA interference (RNAi) therapy are being clinically evaluated [2].

Nanotechnology offers distinct features for varied oncological applications including augmentation of the physicochemical and pharmacokinetic properties of therapeutic molecules viz. stability, solubility, mean residence time, tumour accumulation and retention. Targeted drug delivery to a tissue, cell or organelle resulting in sustained or stimulus-triggered drug release. Thus, facilitating the delivery of macromolecular drugs like DNA, small interfering RNA (siRNA), mRNA and protein to intracellular sites of action. Hence, Drug therapeutic index can be augumented by either increasing efficacy and/or reducing toxicity. Drug resistance can be overcome by co-administration of multiple drugs, leading to improved therapeutic efficacy by providing more defined control of the spatiotemporal exposure of each drug and the delivery of appropriate drug proportion to the target

*Address correspondence to this author at the Department of Pharmaceutical Sciences & Drug Research, Punjabi University, Patiala, India;
E-mail: dimplechopra24@yahoo.co.in

ISSN: 1929-2260 / E-ISSN: 1929-2279/19

site. This also includes transcellular transport of drugs across tight epithelial and endothelial barriers like gastrointestinal tract and the blood–brain barrier. Therapeutic agents can be combined with imaging modalities for more sensitive cancer diagnosis, imaging, visualization and/or real-time feedback on the *in vivo* efficacy of a therapeutic agent. This can be further supplemented by new approaches for the development of synthetic vaccines, miniaturized medical devices for cancer diagnosis, drug screening and delivery. Nanomaterials like gold nanoshells, nanorods and iron oxide nanoparticles exhibit inherent therapeutic properties upon appropriate stimulation by radiation, heat or magnetic field [2, 3].

Liposomal doxorubicin (LD); Doxil and Myocet were the first category of therapeutic nanoparticles to receive clinical approval for cancer treatment along with other lipid-based nanoparticles [4]. They still denote a large share of clinical-stage nanotherapeutics. Although encapsulating drugs in liposomes has been broadly shown to improve PK and biodistribution, as yet no marketed liposomal therapeutic agents have exhibited an overall survival (OS) benefit when directly compared with the conventional parent drug [5].

The recent phase III results of liposomal cytarabine– daunorubicin (Vyxeos; also known as CPX-351) compared with the standard care regimen of daunorubicin and cytarabine in patients with high-risk acute myeloid leukaemia, showed improved overall survival of 9.56 months versus 5.95 months. In late 2016, this fact was encouraging for the field of cancer nanomedicine and regulatory filing for the approval of Vyxeos. Paclitaxel containing albumin nanoparticles (nab-paclitaxel; Abraxane) was the second class of nanomedicines to be commercialized. The nab platform enables formulation of hydrophobic drugs while largely mitigating the need to use toxic excipients. The result may be a better tolerated drug that can be used at higher doses and administered more quickly, thus enabling a higher drug C max and plasma area under the curve (AUC). Upon intravenous infusion, nab-paclitaxel rapidly dissociates into its albumin and paclitaxel constituents and has not been demonstrated to substantially alter the PK and biodistribution of parent molecule.

A dosing schedule of every-3-week of nab-paclitaxel was found superior to paclitaxel in terms of time to progression and response rate. However, once per week dosing did not show similar response in progression free survival and moreover resulted in increased toxicity in patients with breast cancer [6]. Two classes of novel cancer nanotherapeutics include Polymeric micelles like, Genexol-PM21, NK105 and Polymeric nanoparticles for example, CRLX101, BIND-014 and AZD-2811 Accurin [7-9]. In recent past, disappointing clinical results have been reported for BIND-014, CRLX101 and NK105, emphasizing the need to redesign development strategies, including potential patient selection to recognize those most likely to respond to nanotherapeutics [9]. Inorganic nanomaterials for example gold nanoshell, iron oxide NP and hafnium oxide NP are also being investigated for use in cancer patients, with the iron oxide NP-based NanoTherm already marketed in Europe for glioblastoma [10-13].

Nanoparticles are potential carriers not only for conventional chemotherapeutics but also for novel molecularly targeted anticancer therapeutics like antisense oligonucleotides, small interfering RNA (siRNA), messenger RNA (m-RNA) and DNA inhibitor oligonucleotides [10, 14-16]. The first therapeutic knockdown in humans by polymeric nanoparticle-based systemic siRNA delivery was reported by Davis *et al* (2010) [16].

The use of viral nanoparticles for therapeutic delivery has been enabled by genetic and chemical engineering techniques [17]. This include the use of adeno virus, approved by the European Union for lipase deficiency, lentivirus in numerous clinical trials for cell-based gene therapy and immunotherapy of several diseases including cancer. Engineered plant viruses for example, tobacco mosaic virus and potato virus X have been used for cancer therapy in animal models [18-21]. With their endogenous origin and organ tropism, exosomes have also been proposed for carrying anticancer payloads to target tumours [22]. Novel inorganic NPs such as nanodiamond and graphene have also received considerable attention for cancer therapy [23].

There has been paradigm shift in design of nanomedicine. Theranostic nanomedicine offers a promising strategy by merging diagnostic and therapeutic functions into a single NP formulation. It not only monitors the pharmacokinetics of therapeutics but also progression of disease, giving important insights into heterogeneities within tumours and between patients for personalized treatment in future [24].

By co-delivering multiple active pharmaceutical ingredients (APIs), NPs have also facilitated synergistic

cancer therapy and avoided some mechanisms of drug resistance, as evidenced by co-administration of doxorubicin and antisense oligonucleotides in liposomes targeting MRP1 and BCL2 of NSCLC tumor model [25]. Another example is co-administration of doxorubicin and disulfiram in polymeric micelles for treatment of drug resistant breast cancer. In addition to drug delivery, nanotechnology is gaining importance in the area of cancer immunotherapy. NPs have become increasingly attractive as potent antigen or adjuvant carriers for the preparation of synthetic vaccines, with enhanced tissue penetration and/or access to lymphatics, preferential uptake by antigen presenting cells, sustained release of antigens or adjuvants and NP-mediated phagosome escape of antigens for cross-presentation [26-28].

Nanotechnology holds great potential for addressing the shortcomings associated with biologics, including mAbs that are used for cancer immunotherapy. For example, the administration of biologic drugs can induce the formation of antidrug antibodies (ADAs) that may adversely affect their safety and efficacy. In recent past, engineered tolerogenic nanoparticles carrying rapamycin have shown to abolish the development of ADAs for biologics in rodents and non-human primates. Human clinical trials are currently in pipeline. Our expectation is that by gaining a deeper insight into nano–bio interactions with personalization of nanomedicines, and through the use of nanotechnology to existing and emerging therapeutic modalities, their will be beginning of realization of true potential of nanomedicine in cancer [29, 30].

2. IMPACT OF NANOPARTICLE PROPERTIES ON SYSTEMIC DELIVERY TO TUMOURS

Nanoparticles (NPs) can be made from diverse materials with numerous physicochemical properties for example particle size, geometry, surface attributes, elasticity and stiffness. Moreover they can be modified with a numerous targeting ligands of diverse surface density. NP properties affect physiological processes involved in the delivery of drug to tumour tissues, involving blood circulation, serum protein interactions, biodistribution, extravasation to tumour microenvironment via leaky tumour vessels and tumor tissue infiltration, tumour cell targeting and intracellular trafficking. NPs can also be formulated to control the release profile of drug payloads [2, 31, 32].

Along with enormous progress in the area of cancer nanomedicine, the challenges and opportunities that lie ahead have been gradually realized. Foremost, the complexity and the heterogeneity of tumours make it clear that careful patient stratification is required to categorize those most likely to be cured from a given nanotherapy [33]. This is quite similar to the targeted therapies approved or under clinical evaluation for use in specific biomarker-defined patient populations. Most therapeutic NPs for solid tumour treatment are administered systemically; they accumulate in the tumour through the enhanced permeability and retention (EPR) effect, which is generally thought to be the product of leaky tumour vasculature and poor lymphatic drainage. However, this interpretation of EPR is somewhat oversimplified, as multiple biological steps in the systemic delivery of NPs can influence this effect, such as NP–protein interaction, blood circulation, extravasation into and interaction with the perivascular tumour microenvironment (TME), tumour tissue penetration and tumour cell internalization [34]. NP properties such as particle size, particle shape, surface attributes, elasticity, stiffness, porosity, composition and targeting ligand can influence these biological processes, thus determining the EPR effect and therapeutic outcomes.

Thus, it is important to point out that most of our understanding of NP behaviour *in vivo* is based on animal data, and its translation to NP behaviour in humans remains mostly unexplored [35]. Although numerous studies have examined the pharmacokinetics (PK) of nanotherapeutics across species in preclinical and clinical studies, relatively few have interrelated data across species to determine whether and how NP safety and efficacy in humans can be better predicted from preclinical animal models [36]. Considerable success has been achieved in this field, but the main obstacles to nanomedicine becoming a novel paradigm in cancer therapy stem from the intricacies and heterogeneity of tumour, an inadequate understanding of nano–bio interactions and the challenges regarding chemistry, manufacturing and controls required for clinical translation and commercialization [37]. Nanomedicines are extensively employed in cancer therapy. Meel *et al*. (2019) [1] have proposed four strategic directions to improve nanomedicine translation and exploitation. (1) Patient stratification has become common practice in oncology drug development. Accordingly, probes and protocols for patient stratification are urgently needed in cancer nanomedicine, to identify individuals suitable for inclusion in clinical trials. (2) Rational drug selection is crucial for clinical and commercial success.

Opportunistic choices based on drug availability should be replaced by investments in modular (pro)drug and nanocarrier design. (3) Combination therapies are the mainstay of clinical cancer care.

The synergism between nanomedicines, pharmacological and physical co-treatments, should be incorporated in multimodal combination therapy regimens. (4) Immunotherapy is transforming the treatment of cancer. Nanomedicines can alter the behaviour of myeloid and lymphoid cells, thereby augumenting anticancer immunity and immunotherapy. Either alone or in combination these four strategies provide the basis for rational development of smart cancer nanomedicine.

3. BRIDGING THE GAP BETWEEN BIO-NANOSCIENCE AND CANCER NANOMEDICINE

The interface of bio-nano science and cancer medicine is an area experiencing much progress but also beset with controversy. Fundamental concepts of the field primarily the enhanced permeability and retention (EPR) effect leading to tumor targeting and accumulation, and even the basis of "nano" in cancer medicine-are hotly debated. Simultaneous advances in allied disciplines like "immuno-oncology" are changing our understanding and perspective on treatment of cancer.

Herein, one should (i) reconsider how cancer is usually treated in the clinic and how it can be improved with nanomedicine; (ii) examine the current discussion on the relevance of the EPR effect and tumor targeting; (iii) Focus on ways to improve next-generation nanomedicines (iv) deliberate on the concept of working in unison with biology.

While discussing these controversies, challenges, emerging concepts, and opportunities, we explore new directions for the field of cancer nanomedicine [38].

4. IMMUNOTHERAPEUTICS AND NANOMEDICINE SYNERGISM

Nanomedicine-based tumor targeting is typically achieved via two main mechanisms, i.e., passive and active targeting. Passive targeting relies on the enhanced permeability and retention (EPR) effect [39]. The EPR effect discovered three decades ago, still forms the basis of delivery of nanoparticles and macromolecules to solid tumors [40]. Moreover it supported increased microvascular permeability of macromolecules into tumours in comparison to normal tissues, supporting the use of large-size medicinal agents in cancer treatment. Active targeting relies on the decoration of nanoparticles with targeting ligands, such as antibodies or peptides, which specifically recognize receptors overexpressed at the pathological site.

Both strategies have associated pros and cons with respect to specific cell delivery, overall targeting efficiency, formulation complexity and translational potential [41]. Instead of directly killing cancer cells, nanomedicines can combat malignancies by modulating antitumor immune responses. This can be achieved by developing nanomedicines which (1) target cancer cells to elicit immunogenic cell death; (2) target immune cells, such as macrophages, dendritic cells and T cells, or immunosuppressive pathways in the tumor immune microenvironment; and (3) target the peripheral immune system, comprising lymph nodes and spleen [42-46]. There is ample evidence to support the fact that nanomedicines can potentiate antitumor immunity and synergize with established immunotherapeutics to improve response rates and overall survival time of cancer patients [47].

5. CONCLUSION

Nanoparticles have been widely reported as carriers for chemotherapeutics, thus Cancer nanomedicine has profound potential to revolutionize medicine. We must improve our understanding of tumour heterogeneity and identifying EPR markers which will enable selection of patients maximally responsive to nanotherapies.

A full understanding of nano–bio interactions, systemic transport of NPs to tumour cells and targeting of NPs to the Tumor microenvironment or premetastatic niche will lead to safer and more efficacious nanotherapeutics. Considering the challenges of controllable, reproducible and scalable nanoparticle preparation, characterization and evaluation, will facilitate clinical development. Although most approved nanomedicines have used conventional drugs as payloads, it is anticipated that further generation of nanomedicines will incorporate new molecular entities for example, kinase inhibitors and novel classes of therapeutic agent for example, siRNA, mRNA and gene editing. In summary, we are rapidly acquiring a much deeper understanding of the challenges and opportunities presented by cancer nanomedicine. This Review has explored the importance of the convergence of nanotechnology and

tumour biology for more successful development and clinical translation of nanotherapeutics. We expect that nanomedicines will shift the paradigm of cancer treatment, and that the true goal of cancer nanomedicine — dramatic improvement in patient survival — will become a reality in future.

REFERENCES

[1] van der Meel R, Sulheim E, Shi Y. *et al.* Smart cancer nanomedicine. Nat Nanotechnol 2019; 14: 1007-1017. https://doi.org/10.1038/s41565-019-0567-y

[2] Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 2017; 17: 20-37. https://doi.org/10.1038/nrc.2016.108

[3] Zanganeh S, Hutter G, Spitler R, Lenkov O, Mahmoudi M, Shaw A, Pajarinen JS, Nejadnik H, Goodman S, Moseley M, Coussens LM, Daldrup-Link HE. Iron oxide nanoparticles inhibit tumour growth by inducing pro-inflammatory macrophage polarization in tumour tissues. Nat Nanotechnol. 2016; 11: 986-994. https://doi.org/10.1038/nnano.2016.168

[4] Barenholz Y. Doxil®—the first FDA-approved nano-drug: lessons learned. J Control Release 2012; 160: 117-134. https://doi.org/10.1016/j.jconrel.2012.03.020

[5] Petersen GH, Alzghari SK, Chee W, Sankari SS, La-Beck NM. Meta-analysis of clinical and preclinical studies comparing the anticancer efficacy of liposomal versus conventional nonliposomal doxorubicin. J Control Release 2016; 232: 255-264. https://doi.org/10.1016/j.jconrel.2016.04.028

[6] Rugo HS, *et al.* Randomized phase III trial of paclitaxel once per week compared with nanoparticle albumin-bound nab-paclitaxel once per week or ixabepilone with bevacizumab as first-line chemotherapy for locally recurrent or metastatic breast cancer: CALGB 40502/NCCTG N063H (Alliance). J Clin Oncol 2015; 33: 2361-2369. https://doi.org/10.1200/JCO.2014.59.5298

[7] Kato K, *et al.* Phase II study of NK105, a paclitaxel-incorporating micellar nanoparticle, for previously treated advanced or recurrent gastric cancer. Invest New Drugs 2012; 30: 1621-1627. https://doi.org/10.1007/s10637-011-9709-2

[8] Ahn HK, *et al.* A phase II trial of Cremorphor EL-free paclitaxel (Genexol-PM) and gemcitabine in patients with advanced non-small cell lung cancer. Cancer Chemother Pharmacol 2014; 74: 277- 282. https://doi.org/10.1007/s00280-014-2498-5

[9] Clark AJ, *et al.* CRLX101 nanoparticles localize in human tumors and not in adjacent, nonneoplastic tissue after intravenous dosing. Proc Natl Acad Sci USA 2016; 113: 3850-3854. https://doi.org/10.1073/pnas.1603018113

[10] Ashton S, *et al.* Aurora kinase inhibitor nanoparticles target tumors with favorable therapeutic index *in vivo*. Sci Transl Med 2016; 8: 325ra17. https://doi.org/10.1126/scitranslmed.aad2355

[11] Hirsch LR, *et al.* Nanoshell-mediated near-infrared thermal therapy of tumors under magnetic resonance guidance. Proc Natl Acad Sci USA 2003; 100: 13549-13554. https://doi.org/10.1073/pnas.2232479100

[12] Maier-Hauff K, *et al.* Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam radiotherapy on patients with recurrent glioblastoma multiforme. J Neurooncol 2011; 103: 317-324. https://doi.org/10.1007/s11060-010-0389-0

[13] Maggiorella L, *et al.* Nanoscale radiotherapy with hafnium oxide nanoparticles. Future Oncol 2012; 8: 1167-1181. https://doi.org/10.2217/fon.12.96

[14] Dritschilo A, *et al.* Phase I study of liposome-encapsulated craf antisense oligodeoxyribonucleotide infusion in combination with radiation therapy in patients with advanced malignancies. Clin Cancer Res 2006; 12: 1251-1259. https://doi.org/10.1158/1078-0432.CCR-05-1260

[15] Elazar V, *et al.* Sustained delivery and efficacy of polymeric nanoparticles containing osteopontin and bone sialoprotein antisenses in rats with breast cancer bone metastasis. Int J Cancer 2010; 126: 1749-1760. https://doi.org/10.1002/ijc.24890

[16] Davis ME, *et al.* Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles. Nature 2010; 464: 1067-1070. https://doi.org/10.1038/nature08956

[17] Yildiz I, Shukla S, Steinmetz NF. Applications of viral nanoparticles in medicine. Curr Opin Biotechnol 2011; 22: 901-908. https://doi.org/10.1016/j.copbio.2011.04.020

[18] Yla-Herttuala S. Endgame: glybera finally recommended for approval as the first gene therapy drug in the European Union. Mol Ther 2012; 20: 1831-1832. https://doi.org/10.1038/mt.2012.194

[19] Naldini L. Gene therapy returns to centre stage. Nature 2015; 351-360. https://doi.org/10.1038/nature15818

[20] Shukla S, DiFranco NA, Wen AM, Commandeur U, Steinmetz NF. To target or not to target: active versus passive tumor homing of filamentous nanoparticles based on potato virus X. Cell Mol Bioeng 2015; 8: 433-444. https://doi.org/10.1007/s12195-015-0388-5

[21] Czapar AE, *et al.* Tobacco mosaic virus delivery of phenanthriplatin for cancer therapy. ACS Nano 2016; 10: 4119-4126. https://doi.org/10.1021/acsnano.5b07360

[22] Batrakova EV, Kim MS. Using exosomes, naturally-equipped nanocarriers, for drug delivery. J Control Release 2015; 219: 396-405. https://doi.org/10.1016/j.jconrel.2015.07.030

[23] Chow EK, *et al.* Nanodiamond therapeutic delivery agents mediate enhanced chemoresistant tumor treatment. Sci Transl Med 2011; 3: 73ra21. https://doi.org/10.1126/scitranslmed.3001713

[24] Van der Meel R, Lammers T, Hennink WE. Cancer nanomedicines: oversold or underappreciated? Expert Opin Drug Deliv 2017; 14: 1-5. https://doi.org/10.1080/17425247.2017.1262346

[25] Garbuzenko OB, *et al.* Inhibition of lung tumor growth by complex pulmonary delivery of drugs with oligonucleotides as suppressors of cellular resistance. Proc Natl Acad Sci USA 2010; 107: 10737-10742. https://doi.org/10.1073/pnas.1004604107

[26] Kreiter S, *et al.* Mutant MHC class II epitopes drive therapeutic immune responses to cancer. Nature 2015; 520: 692-696. https://doi.org/10.1038/nature14426

[27] Kranz LM, *et al.* Systemic RNA delivery to dendritic cells exploits antiviral defence for cancer immunotherapy. Nature 2016; 534: 396-401. https://doi.org/10.1038/nature18300

[28] Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines - a new era in vaccinology. Nat Rev Drug Discov 2018; 17: 261-279. https://doi.org/10.1038/nrd.2017.243

[29] Oberli MA, *et al.* Lipid nanoparticle assisted mRNA delivery for potent cancer immunotherapy. Nano Lett 2017; 17: 1326-1335. https://doi.org/10.1021/acs.nanolett.6b03329

[30] Sahin U, *et al*. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017; 547: 222-226. https://doi.org/10.1038/nature23003

[31] Nel AE, *et al*. Understanding biophysicochemical interactions at the nano-bio interface. Nat Mater 2009; 8: 543-557. https://doi.org/10.1038/nmat2442

[32] Mahmoudi M, *et al*. Protein-nanoparticle interactions: opportunities and challenges. Chem Rev 2011; 111: 5610-5637. https://doi.org/10.1021/cr100440g

[33] Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. Adv Drug Deliv Rev 2014; 66: 2-25. https://doi.org/10.1016/j.addr.2013.11.009

[34] Hrkach J, *et al*. Preclinical development and clinical translation of a PSMA-targeted docetaxel nanoparticle with a differentiated pharmacological profile. Sci Transl Med. 2012; 4: 128ra39. Firstin-human testing of a targeted, controlled-release polymeric NP for cancer chemotherapy. https://doi.org/10.1126/scitranslmed.3003651

[35] Eliasof S, *et al*. Correlating preclinical animal studies and human clinical trials of a multifunctional, polymeric nanoparticle. Proc Natl Acad Sci USA 2013; 110: 15127-15132. https://doi.org/10.1073/pnas.1309566110

[36] Zuckerman JE, *et al*. Correlating animal and human phase Ia/Ib clinical data with CALAA-01, a targeted, polymer-based nanoparticle containing siRNA. Proc Natl Acad Sci USA 2014; 111: 11449-11454. https://doi.org/10.1073/pnas.1411393111

[37] Ritz S, *et al*. Protein corona of nanoparticles: distinct proteins regulate the cellular uptake. Biomacromolecules 2015; 16: 1311-1321. https://doi.org/10.1021/acs.biomac.5b00108

[38] Björnmalm M, Thurecht KJ, Michael M, Scott AM, Caruso F. Bridging Bio-Nano Science and Cancer Nanomedicine. ACS Nano 2017; 11(10): 9594-9613. https://doi.org/10.1021/acsnano.7b04855

[39] Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res 1986; 46: 6387-6392.

[40] Maeda H. Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. Adv Drug Deliv Rev 2015; 91: 3-6. https://doi.org/10.1016/j.addr.2015.01.002

[41] Kearney CJ, Mooney DJ. Macroscale delivery systems for molecular and cellular payloads. Nat Mater 2013; 12: 1004-1017. https://doi.org/10.1038/nmat3758

[42] Lammers T, Kiessling F, Ashford M, Hennink W, Crommelin D, Storm G. Cancer nanomedicine: is targeting our target? Nat Rev Mater 2016; 1: 16069. https://doi.org/10.1038/natrevmats.2016.69

[43] Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, Chan WC. Analysis of nanoparticle delivery to tumours. Nat Rev Mater 2016; 1: 16014. https://doi.org/10.1038/natrevmats.2016.14

[44] Wang C, Ye Y, Hu Q, Bellotti A, Gu Z. Tailoring biomaterials for cancer immunotherapy: Emerging trends and future outlook. Adv Mater 2017; 29: 1606036. https://doi.org/10.1002/adma.201606036

[45] Jiang W, Von Roemeling CA, Chen Y, Qie Y, Liu X, Chen J, Kim BY. Designing nanomedicine for immuno-oncology. Nat Biomed Eng 2017; 1: 0029. https://doi.org/10.1038/s41551-017-0029

[46] Sun Q, Barz M, De Geest BG, Diken M, Hennink WE, Kiessling F, Lammers T, Shi Y. Nanomedicine and macroscale materials in immuno-oncology. Chem Soc Rev 2019; 48: 351-381. https://doi.org/10.1039/C8CS00473K

[47] Irvine DJ, Hanson MC, Rakhra K, Tokatlian T. Synthetic nanoparticles for vaccines and immunotherapy. Chem Rev 2015; 115: 11109-11146. https://doi.org/10.1021/acs.chemrev.5b00109

Received on 10-12-2019 Accepted on 25-12-2019 Published on 30-12-2019

DOI: http://dx.doi.org/10.30683/1929-2279.2019.08.10