

Jacobs Journal of Cancer Science and Research

Review Article

A Review Article on Clinical Trials on Hybrid Drugs and Nanohybrid Technologies in Drug Development that Combat Cancer

Timothy Allen, MD, Ph.D^{*1}, Giridhar M.N.V, MD,MBA¹, Ghazaleh Shoja E Razavi MD²

¹Global Allied Pharmaceutical, Center for Excellence in Research & Development, USA.

²Dir. Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, USA.

**Corresponding author: Dr. Timothy Allen, MD, PhD, Global Allied Pharmaceutical, Center for Excellence in Research and Development, USA, Tel: 321-945-4283; Email: Timothy.Allen@gapsos.com*

Received: 02-26-2015

Accepted: 04-28-2015

Published: 06-01-2015

Copyright: © 2015 Timothy

Abstract

Cancer is one of highly prevalent disease worldwide that affects different organs of the body leading to rapid and uncontrolled division of cells forming a mass of tumor cells. There are several conventional therapies available for cancer diagnosis like Xray, magnetic resonance, CT, tomography, B ultrasound, endoscopy and cancer treatment such as radiotherapy, chemotherapy, surgery. but there is growing need for a novel drug delivery system which can target only cancerous cell and not affecting healthy cells. Nanotechnology has come up with one of the drug delivery system to work at nano scale based in the area of bioengineering, medicine and pharmacology. Based on previous experience engineer are trying to evolve a new treatment system which can reduced the side effects occurring due to conventional procedures. Hybrid drug and Nanohybrid technology are the most advance technology for the effect treatment of Cancer. Hybrid drugs are being designed to combine two anti-cancer agents so that they can act more effectively and nanodrugs are being developed to improve delivery of the therapeutic agent to the cancerous site without causing side effects to healthy cells. In this review, we discussed several in vitro research and clinical research conducted on several hybrid drugs (p63-53o and Specific and Non-genetic IAP-dependent Protein Eraser, and Hybrid 9) and nanodrugs such as pegylated liposomal doxorubicin, albumin-bound paclitaxel, and N-(2 hydroxypropyl) methacrylamide-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer-Mesochlorin e6), which showed them to be effective treatment gaining importance in cancer therapeutics.

Keywords: Hybrid Drugs; Cancer; Nanocancer; Liposome Nanoparticles; Nano Hybrid Technology; Advance Chemotherapy; Nanotechnology

Abbreviations

HSPC: Hydrogenated Phosphatidylcholine;
FDA: Food And Drug Administration;
Eggpg: Egg Yolk Phosphatidylglycerol;
DSPC: 1, 2-Distearoyl-Glycero-3-Phosphocholine;
PEG: Polyethylene Glycol;

HPMA: N-(2 Hydroxypropyl) Methacrylamide;
PLA: Poly (Lactic Acid);
PLGA: Poly(Lactic-Co-Glycolic Acid);
PAMAM: Polyamidoamine;
TNF: Tumor Necrosis Factor;
SNIPER: Specific and Non-Genetic IAP-Dependent Protein Eraser;
Ciap1: Cellular Inhibitor of Apoptosis Protein 1;
E α : Estrogen Receptor A;
POSS: Polyhedral Oligomeric silsesquioxane;
PLD: Pegylated Liposomal Doxorubicin;
STS: Soft Tissue Sarcoma;
MBC: Metastatic Breast Cancer;
PDT: Photodynamic Therapy;
NSCLC: Non-Small-Cell Lung Cancer;
MTD: Maximum Tolerated Dose;
Nab-Paclitaxel: Nanoparticle Albumin-Bound Paclitaxel

Introduction

Cancer medically known as malignant neoplasia, is a group of diseases which involves unregulated cell growth. Malignant cells grow and divide uncontrollably, forming malignant tumors, which may spread to different parts of the body. There are over 200 different types of cancers that are known to affect human [1].

The American Cancer Society reported that total of 1,660,290 new cancer cases and 580,350 cancer deaths occurred in the U.S. in 2013. The cancer death rates decreased by 1.5% per year in women and by 1.8% per year in men. Death rates for major cancer sites (colorectal, lung, breast, and prostate) continue to decline due to recent advance in diagnosis and treatment in cancer at all stages. As per the facts provided by American cancer society inc, a decline of approximately 40% is seen in death cases for prostate cancer and 30 % for cancer related to other site like lung cancer, breast cancer and colon cancer is observed since 1991. Although gastric cancer is still an area needs more improvement. [2] As per the facts available for 1980 to 2005, only 3.6 to 4.9% decline is observed in mortality rate for both men and women, which is unaccountable [3].

Common treatments used for cancer are surgery, radiation therapy and chemotherapy. The chances of surviving the disease are affected by the location and type of the cancer and also on the extent of disease at the start of treatment [4].

Surgery: The primary method of treatment of most isolated solid cancers is surgery and may play a role in prolongation of survival. For some types of cancer this is all that is needed to eliminate the cancer [9].

Radiation therapy: It uses ionizing radiation, such as gamma-rays to either improve or cure the symptoms of cancer [5-7]. Radiation therapy is usually provided in addition to chemo-

therapy and surgery but may be used alone for certain cancer types, such as head and neck cancer [8].

Chemotherapy: Another method available for cancer treatment is chemotherapy which involves delivering of anti-cancer drugs that kills rapidly dividing cancer cells. It may include use of a single drug or combination of several drugs (polychemotherapy) [10].

However, there are several side effects associated with these treatment methods such as surgery, chemotherapy and radiotherapy affects normal cells in addition to cancerous cells and may lead to several other side effects and toxicities.

Surgery a common therapeutic option leads to several post-operative complications such as pain, nausea, vomiting [11-13] and non-healing wounds [14].

Several side effects of radiotherapy include hair loss, skin irritation, oral mucositis, fatigue, loss of taste and increase risk of post-operative complications [7].

The major side effect of chemotherapy is that in addition to targeting tumor cells, it also kills normal rapidly dividing cells further resulting in other side effects such as alopecia (hair loss), myelosuppression (decreased production of blood cells), and mucositis [7].

Hybrid Drugs

Cancer is a complex disease, thus it is unlikely that a single mono functional 'targeted' drug can effectively treat this disease in most advanced stage [16]. Combined drugs that have potential to impact multiple targets simultaneously can control complex disease systems, are the standard of care in cancer treatment, and are less prone to drug resistance. In order to improve the efficiency of using two-drug simultaneously, one approach involves the use of the so-called hybrid drugs. These hybrid drugs comprise the incorporation of two drugs in a single molecule that can exert dual drug action [16].

Hybrid Anticancer Drugs are new therapeutics for cancer which has potential to overcome most of the pharmacokinetic drawbacks encountered with use of conventional anticancer drugs such as doxorubicin [17].

Targeted drug delivery to cell populations of cancer sites is an active area of research today as most of the anti-cancer agents cause side effects on healthy or normal body cells that is non-cancerous cells [18].

This article will reflect on several hybrid technologies and will review clinical trials on hybrid drugs as well as hybrid technologies that are being used to develop anticancer agents. The review will focus on efficacy and benefits of hybrid drugs in combating cancer. Several hybrid drugs in use and under trials

include nanocancer drugs [19].

As we have already discussed that major side effect of chemotherapy is killing of normal cells in addition to tumor cells by chemotherapeutic agents. So, anticancer drugs have been combined with a delivery system which helps them to target the disease site, thus reduced damage to normal cells. These delivery systems have been called as hybrid drug delivery systems. Nanotechnology is a multidisciplinary field that uses principles from chemistry, engineering, physics, and biology to fabricate nanoscale devices with a size range of 1-100nm. Benefits of nanotechnology are in the areas of imaging, detection, and therapy of disease. One area where nanotechnology has the potential to make a significant impact is drug delivery [28].

Several nanoscale drug delivery systems are already available in the clinical settings. Nanoscale drug delivery systems encapsulate therapeutics agents such as peptides, nucleic acids, protein-based drugs, and small molecules (hydrophilic and/or hydrophobic). Encapsulation of these drug molecules improves their stability and solubility [29]. Encapsulated drug is released in controlled from nanocarriers to maintain a drug concentration within a therapeutic window [30].

Engineering of the surface of the nanocarrier is done to increase its circulation in the blood and to enhance the biodistribution, and attaching of targeting ligands to the surface of nanocarrier can result in enhanced uptake by target tissues [31-32].

We will discuss several nanoparticle drug delivery systems that are gaining wide acceptance in cancer therapy, such as liposome nanoparticles, polymeric drug conjugate, polymeric nanoparticles, micelles, dendrimers, proteins, biological nanoparticles, inorganic nanoparticles [33-36].

Liposome Nanoparticles

Lipids form nanoparticle vesicles through the self-assembly of amphiphilic lipids and excipients. The lipids form a bilayer based on hydrophobic interactions in continuous parallel packing, with the hydrophilic head groups positioned towards the aqueous environment. Hydrophilic molecules can be encapsulated in the inner aqueous phase while hydrophobic molecules can be carried in the hydrophobic domains of the lipid bilayer. Physicochemical properties of liposome can be precisely changed to control surface charge, functionality, and size by simply mixing commercially available lipid molecules. This offers a significant advantage over other carriers that require much more controlled synthesis steps and additional chemical modifications. Lipids such as HSPC (hydrogenated phosphatidylcholine from soybean lecithin), EggPG (egg yolk phosphatidylglycerol) and DSPC (1,2-distearoyl-glycero-3-phosphocholine) have been approved by the U.S. Food and Drug Administration (FDA) [37].

Doxil, a pegylated liposome loaded with doxorubicin has been used clinically to treat multiple types of cancers. Several other drugs such as camptothecin, docetaxel, and bryostatins-1 has been delivered through nanosomes (small liposomes, <100 nm) [38-43].

Polymer-Drug Conjugates Nanoparticles

They are formed through side-chain grafting of drugs to polymer chains which allows them to deliver high doses of chemotherapeutic drugs. Polymer-drug conjugates are currently in phase III clinical trials. The first synthetic polymer-anticancer drug that entered clinical trials was N-(2-hydroxypropyl) methacrylamide (HPMA)-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer (PK1) [34]. Polyaminoacids, are another polymer-drug conjugates grafted with drugs on the side chains that have been identified to possess high drug loading and efficacy [42]. For Example: polyglutamate-glycine-camptothecin (CT-2106) [43-44].

Polymeric Nanoparticles

They are the most effective nanocarriers for prolonged drug delivery. Such as polyalkylcyanoacrylate-based nanoparticles releasing doxorubicin, use of poly(lactic acid)/poly(lactic-co-glycolic acid) (PLA/PLGA) and PEG block copolymer as "long-circulating nanoparticles" [45]. Some common polymers used for nanoparticles formation include dextran, poly(lactic acid) (PLA), and chitosan [46].

Micelle Nanoparticles

Micelles may be composed of lipids or other amphiphilic molecules, such as polyamino acids or polymers, and self-assemble into small nanoparticles composed of a hydrophobic core. Hydrophobic drugs have been delivered using micelles as drug delivery carriers [47]. Some of micellar formulations in clinical trials are Genexol-PM, NK105, NC-6004, NK911 [48-51].

Dendrimer Nanoparticles

Dendrimers (5-10 nm) possess well-defined branching architectures and surface functional groups available for further modification. They have remarkable pharmacokinetic properties and molecular monodispersity for systemic drug delivery [52]. For example: methotrexate polyamidoamine (PAMAM) [53].

Protein Nanoparticles

Development of albumin bound drug nanoparticles (~130 nm) has recently made a big impact on protein-based drug delivery systems. Albumin-bound paclitaxel (Abraxane, ABI-008,) has been approved by the FDA in 2005 for metastatic breast

cancer therapy, as well as in clinical trials for targeting other types of cancer [54].

Biological Nanoparticles

Biological nanoparticles such as bacteria with different sizes and shapes that encapsulate essential components of the cytoplasm as well as hydrophilic and hydrophobic molecules. "Nanocell" which consists of anucleate globular bacteria (~400 nm), developed by EnGeneIC Pty Ltd is an example of biological nanoparticles that is being investigated for cancer therapy [37].

Inorganic Nanoparticles

Inorganic nanoparticles are metal-based and have the potential to be synthesized with near monodispersity. Intrinsic properties of inorganic nanoparticles have been explored for therapy. Metal nanoparticles are currently under clinical trials, such as iron oxide nanoparticles coated with aminosilane (Nanotherm M01). CytImmune Sciences, Inc. have developed Aurimmune (CYT-6091), tumor necrosis factor (TNF)-alpha, bound to PEG-coated gold nanoparticles (~27 nm) for solid tumor therapy [56].

Nanohybrid technologies

Now, we will discuss results of several clinical trials on hybrid drugs and nanohybrid technologies. Researchers conducted an *in vitro* research on a series of novel 1,2,4-trioxane-based hybrids incorporating egonol and/or ferrocene fragments against the multidrug-resistant P-glycoprotein-over-expressing CEM/ADR5000 cells.

A remarkable cytotoxicity toward CCRF-CEM cells (IC₅₀ of 0.25, 0.07, and 0.18 μ M, respectively) was shown by novel hybrids 9 (1,2,4-trioxane-ferrocene), 7 (1,2,4-trioxane-ferrocene-egonol), and 11 (artesunic acid-egonol). Hybrid 9 containing a ferrocene fragment and 1,2,4-trioxane has shown to be the most effective among the studied hybrids against the tested multidrug-resistant leukemia CEM/ADR5000 cells (IC₅₀ of 0.57 μ M) [57].

The regulation of p53 (tumor suppressor) activity differs significantly from that of p63 and p73. The tumor suppressive activity of p53 was enhanced by constructing six recombinant adenoviruses that encode hybrid proteins with three functional domains derived from either TAp63 γ or p53. The role of these hybrid molecules in suppressing tumorigenesis was evaluated using *in vivo* and *in vitro* models. The hybrid named p63-530 was found to be the most potent activator of apoptosis in human cancer cells.

Researchers have developed SNIPER (Specific and Non-genet-

ic IAP-dependent Protein ERaser), which is composed of two ligands connected by a linker, one is a ligand for a target protein and the other is cellular inhibitor of apoptosis protein 1 (cIAP1). Researchers have used tamoxifen as a ligand for estrogen receptor α (ER α) in a novel SNIPER to knockdown ER α protein. SNIPER(ER) induced degradation of ER α and inhibited expression of pS2 gene in breast cancer MCF-7 cells. Following the ER α degradation, the SNIPER(ER)-treated MCF-7 cells undergo rapid cell death [59]. Kawamoto and his colleagues conducted *in vivo* and *in vitro* research on the newly designed HER2-lytic hybrid peptide that lead to cancer cell death via membrane lysis. High cytotoxicity of HER2-lytic hybrid peptide was observed against breast and cancer cell lines that are resistant to lapatinib and/or trastuzumab *in vivo* and *in vitro* [60]. Polyhedral Oligomeric Silsesquioxane (POSS)-F68 hybrid vesicles (average diameter of 700 nm) are another hybrid drug delivery systems that have been used for making doxorubicin and folic acid loaded vesicles. POSS-F68 vesicles in combination with a chemotherapeutic and folic acid have potential for targeted intracellular anti-cancer drug delivery. Flow cytometric and confocal microscopic studies on the endocytosis of the vesicles by HOS and HeLa cells prove that a noncovalent entrapment of excess folic acid in the vesicles through H-bonding can significantly enhance the uptake [61]. Fig 1. Researchers conducted a clinical trial on twenty-eight patients to evaluate the impact of pegylated liposomal doxorubicin (PLD), a formulation with pharmacokinetic differences with respect to doxorubicin (DXR), on quality of life of patients with advanced soft tissue sarcoma (STS) pretreated with DXR. Patients were given 35 mg/2 of PLD every 3 weeks. The study observed Grade 3 toxicity: stomatitis (4%), palmar-plantar erythrodysesthesia (19% of patients), or cutaneous (4%). Progression-free rate at 3 and 6 months was 48% and 22%, respectively, median overall survival 8.7 months and median progression-free survival 5.8 months. Measurement of patient's quality of life with EORTC QLQ-C30 showed that the therapy didn't worsen the quality [62].

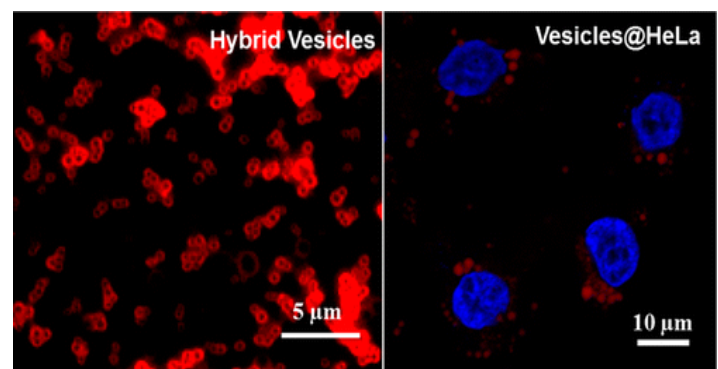


Figure 1. Polyhedral Oligomeric Silsesquioxane (POSS)-F68 hybrid.

A phase III randomized clinical trial was conducted on 509 women's with metastatic breast cancer (MBC) to compare effi-

cacy of PLD and doxorubicin in treatment. Subjects received either doxorubicin 60 mg/m² (every 3 weeks) or PLD 50 mg/m² (every 4 weeks). Efficacy of PLD and doxorubicin in first line therapy for MBC was comparable, with significantly reduced cardiotoxicity, vomiting, neutropenia, alopecia and nausea [63]. Another study on human ovarian OVCAR-3 carcinoma xenografted in female athymic mice was conducted to assess the effectiveness of HPMA-doxorubicin (N-(2-hydroxypropyl) methacrylamide) copolymer-mesochlorin e6 and adriamycin Conjugates in treating ovarian cancer when used in combination with other anticancer therapies including chemotherapy and photodynamic therapy (PDT). OVCAR-3 tumors were suppressed with 13.4 mg/kg (1.5 mg/kg of Mce6 equivalent) dose of HPMA copolymer-Mce6 conjugate (PDTMC) and light doses of 110 J/cm² at 12 and 18h [64].

Phase I Clinical trial of HPMA copolymer-anticancer conjugates, HPMA copolymer-Gly-Phe-Leu-Gly-doxorubicin, with increasing doses up to a maximum-tolerated dose of 320 mg per m² in chemotherapy-resistant patients showed cardiotoxicity, renal elimination (50–75% over the first 24 h), prolonged plasma circulation ($t_{1/2\alpha} = 1.8$ h), an absence of liver accumulation [65-66] and partial responses in patients with breast cancer and non-small-cell lung cancer (NSCLC) were observed in phase II trials [67]. These studies confirmed that HPMA copolymer could be used to deliver more than 20 g per m² of dose without polymer-related immunogenicity and toxicity. Genexol-PM, nontargeted polymeric micellar, was approved as a first-line therapy for NSCL cancer and metastatic breast in Korea in 2006. Genexol-PM is formed of block copolymer PDL-LA (1.75 kDa)-mPEG (2 kDa) micelles (size of ~60 nm) loaded with paclitaxel (~15% (w/w)). This preparation is currently under phase II trial for metastatic pancreatic cancer therapy in the U.S. It showed that maximum tolerated dose (MTD) of Genexol-PM (60 mg kg⁻¹) is three folds higher than that of Taxol (20 mg kg⁻¹).

In Korea, clinical phase II trial evaluated Genexol-PM as a co-therapy with cisplatin for advanced NSCL in contrast to a single agent therapy. The study resulted in stable disease status in more than 30 % of the patients and increased survival of one year in 60 percent patients [68]. An *in vitro* study on use of the anticancer drug-methotrexate-encapsulated with PAMAM dendrimer conjugated chitosan nanoparticles was conducted. The cell viability assay showed that CS-PAMAM may have potential role for the water-insoluble drug delivery because of its low cytotoxicity on cells [69].

Gupta and Hatoum conducted a phase III trial to assess the effects of weekly treatment of nanoparticle albumin-bound paclitaxel ([nab-paclitaxel] ABRAXANE® ABI-007) in combination with carboplatin versus solvent-bound (sb)-paclitaxel in combination with carboplatin given every 3 weeks for first line treatment of non-small-cell lung cancer (NSCLC). The study

showed that weekly treatment with nab-paclitaxel resulted in increased survival of NSCLC patients [70]. Fig 2.

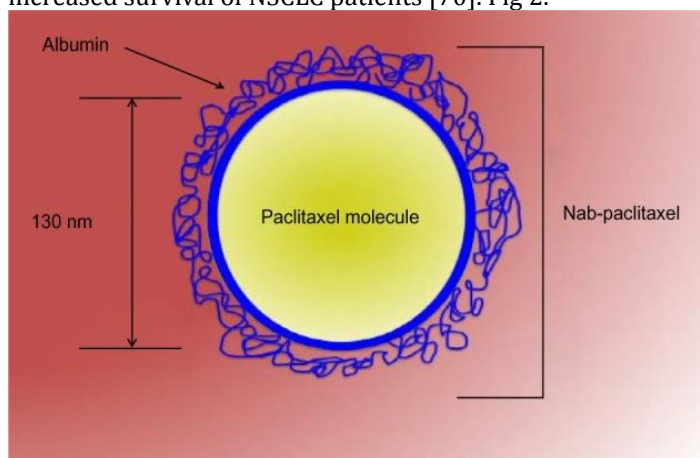


Figure 2. Graphic representation of nanoparticle albumin-bound paclitaxel (nab-paclitaxel).

Discussion

The enhancement of the tumor-targeting efficacy of chemotherapeutic agents is a key issue in management. To overcome this challenge, researchers have developed hybrid drugs and various hybrid technologies (nanohybrid technologies). In this article, we discussed several hybrid drugs including 1,2,4-trioxane-based hybrids incorporating egonol and/or ferrocene, p63-530 SNIPER (Specific and Non-genetic IAP-dependent Protein ERaser) with tamoxifen as a ligand. All these hybrid drugs are currently under *in vitro* and *in vivo* studies and have proved to have higher potential for targeting different forms of cancer. Clinical trials in humans are to be conducted to assess the efficacy and safety of these hybrid drugs in humans.

Further, several nanoscale-based hybrid drugs have been developed of which some are already under clinical use, while others are under different phases of clinical trials. These nanohybrid drugs have been designed to improve the drug delivery system for chemotherapeutics. This article reviewed clinical as well as *in vitro* studies of several nanohybrid technologies such as PLD, nab-paclitaxel and Genexol-PM. All studies showed nanohybrids to be superior method for drug delivery as they enhance efficacy of drug at the targeted site as well reduced side effects to normal body cells.

Conclusion

Hybrid drugs are gaining high acceptance as a treatment option for various forms of cancer. Although, these hybrid drugs have been well studied both *in vitro* and *in vivo* (animals) but may not produce desired therapeutic effects in humans. So, clinical trials in humans are needed to be conducted in order to assess their therapeutic effects, safety as well as their impact

on quality of life of humans.

References

- How many different types of cancer are there? Cancer Research UK: CancerHelp UK. Retrieved 11 May 2012.
- Stacy Simon. Facts and Figures Report: Declines in Cancer Deaths Reach Milestone; American Cancer Society, Inc, 2013.
- Masoud Amiri. The decline in stomach cancer mortality: exploration of future trends in seven European countries. *Eur J Epidemiol.* 2011, 26(1): 23–28.
- Jemal A, Bray, F, Center MM, Ferlay J, Ward E. Global cancer statistics. *CA: a cancer journal for clinicians.* 2011, 61(2): 69–90.
- CK Bomford, IH Kunkler, J Walter. *Walter and Miller's Textbook of Radiation therapy* (6th Ed), 311.
- Radiosensitivity
- Radiation therapy- what GPs.
- James F. Holland, MD. Holland-Frei Cancer Medicine, 6th edition chapter 42, *Principles of Medical Oncology.* BC Decker, 2003.
- Arno J. Mundt, MD. *Frei Cancer Medicine*, 6th edition chapter. 39 *Principles of Radiation Oncology*, BC Decker, 2003.
- Krumbhaar EB. Role of the blood and the bone marrow in certain forms of gas poisoning. *JAMA.* 1919, 72: 39–41.
- Loeser JD, Melzack R. Pain: an overview. *Lancet.* 1999, 353(9164): 1607– 1609.
- Mann A. A continuing postoperative complication: nausea and vomiting - who is affected, why, and what are the contributing factors? A review. *CRNA.* 1998, 9(1): 19–29.
- Watcha MF, White PF. Postoperative nausea and vomiting: its etiology, treatment, and prevention. *Anesthesiology.* 1992, 77(1): 162–184.
- Frank A. Scappaticci, Louis Fehrenbacher, Thomas Cartwright, John D. Hainsworth, William Heim, Jordan Berlin, FairouzKabbinar, William Novotny, Somnath Sarkar, Herbert Hurwitz, Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab, *journal of surgical oncology.* 2005, 91(3):173-180.
- Wang, C, MD, ed. *Clinical Radiation Oncology: Indications, Techniques, and Results.* 2nd Edition. Wiley-Liss, Inc., 2000, 1-5.
- Gediya LK, Njar VC. Promise and challenges in drug discovery and development of hybrid anticancer drugs. *Expert Opin Drug Discov.* 2009, 4(11): 1099-1111.
- Rahman AM, Yusuf SW, Ewer MS. Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation. *Int J Nanomedicine.* 2007, 2(4):567–583.
- Bae YH, Park K. Targeted Drug Delivery to Tumors: Myths, Reality and Possibility. *J. Controlled Release.* 2011, 153(3): 198–205.
- Fortin S, Berube G. Advances in the development of hybrid anticancer drugs. *Expert Opin Drug Discov.* 2013, 8(8): 1029-1047.
- Farokhzad OC, Langer R. Impact of nanotechnology on drug delivery. *ACS Nano.* 2009, 3(1): 16-20.
- Ferrari M. Cancer nanotechnology: opportunities and challenges. *Nat Rev Cancer.* 2005, 5(3): 161–171.
- Fox JL. Researchers discuss NIH's nanotechnology initiative. *Nat Biotechnol.* 2000, 18: 800-821.
- Jiang W, Kim BY, Rutka JT, Chan WC. Advances and challenges of nanotechnology-based drug delivery systems. *Expert Opin Drug Deliv.* 2007, 4(6): 621–633.
- Peppas NA. Intelligent therapeutics: biomimetic systems and nanotechnology in drug delivery. *Adv Drug Deliv Rev.* 2004, 56: 1529–1531.
- Sinha R, Kim GJ, Nie S, Shin DM. Nanotechnology in cancer therapeutics: bioconjugated nanoparticles for drug delivery. *Mol Cancer Ther.* 2006, 5(8): 1909–1917.
- Uchegbu IF. Pharmaceutical nanotechnology: polymeric vesicles for drug and gene delivery. *Expert Opin Drug Deliv.* 2006, 3(5): 629–640.
- Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol Pharm.* 2008, 5(4): 505–515.
- Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. *Mol Pharm.* 2008, 5(4): 505–515.
- Langer R. Drug delivery and targeting. *Nature.* 1998, 392: 5–10.
- Moghimi SM. Recent developments in polymeric nanopar-

- ticle engineering and their applications in experimental and clinical oncology. *Anticancer Agents Med Chem*. 2006, 6(6): 553–561.
31. Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V et al. Biodegradable long-circulating polymeric nanospheres. *Science*. 1994, 263(5153): 1600–1603.
 32. Moghimi SM, Hunter AC, Murray JC. Long-circulating and target-specific nanoparticles: theory to practice. *Pharmacol Rev*. 2001, 53: 283–318.
 33. Chen Y, Huang L. Tumor-targeted delivery of siRNA by non-viral vector: safe and effective cancer therapy. *Expert Opin Drug Deliv*. 2008, 5: 1301–1311.
 34. Gao K, Huang L. Nonviral methods for siRNA delivery. *Mol Pharm*. 2008, 6: 651–658.
 35. Luten J, van Nostrum CF, De Smedt SC, Hennink WE. Biodegradable polymers as nonviral carriers for plasmid DNA delivery. *J Control Release*. 2008, 126: 97–110.
 36. Tseng YC, Mozumdar S, Huang L. Lipid-based systemic delivery of siRNA. *Adv Drug Deliv Rev*. 2009, 61: 721–731.
 37. Frank Alexis, Eric M. Pridgen, Robert Langer, Omid C, Farokhzad. Nanoparticle Technologies for Cancer Therapy, *Handb Exp Pharmacol*. 2010, 197: 55-86.
 38. Cullis PR, Chonn A. Recent advances in liposome technologies and their applications for systemic gene delivery. *Adv Drug Deliv Rev*. 1998, 30: 73–83.
 39. Guo X, MacKay JA, Szoka FC Jr. Mechanism of pH-triggered collapse of phosphatidylethanolamine liposomes stabilized by an ortho ester polyethyleneglycol lipid. *Biophys J*. 2003, 84: 1784–1795.
 40. Kocer A. A remote controlled valve in liposomes for triggered liposomal release. *J Liposome Res*. 2007, 17: 219–225.
 41. Vasey PA, Kaye SB, Morrison R, Twelves C, Wilson P et al. Phase I clinical and pharmacokinetic study of PK1 [N-(2-hydroxypropyl)methacrylamide copolymer doxorubicin]: first member of a new class of chemotherapeutic agents-drug-polymer conjugates. Cancer Research Campaign Phase I/II Committee. *Clin Cancer Res*. 1999, 5: 83–94.
 42. Matsumura Y. Poly (amino acid) micelle nanocarriers in preclinical and clinical studies. *Adv Drug Deliv Rev*. 2008, 60: 899–914.
 43. Homsji J, Simon GR, Garrett CR, Springett G, De Conti R et al. Phase I trial of poly-L-glutamate camptothecin (CT-2106) administered weekly in patients with advanced solid malignancies. *Clin Cancer Res*. 2007, 13: 5855–5861.
 44. Boddy AV, Plummer ER, Todd R, Sludden J, Griffin M, et al. A phase I and pharmacokinetic study of paclitaxel poliglumex (XYOTAX), investigating both 3-weekly and 2-weekly schedules. *Clin Cancer Res*. 2005, 11: 7834–7840.
 45. Gref R, Minamitake Y, Peracchia MT, Trubetskoy V, Torchilin V et al. Biodegradable long-circulating polymeric nanospheres. *Science*. 1994, 263: 1600–1603.
 46. Gref R, Luck M, Quellec P, Marchand M, Dellacherie E, et al. Stealth corona-core nanoparticles surface modified by polyethylene glycol (PEG): influences of the corona (PEG chain length and surface density) and of the core composition on phagocytic uptake and plasma protein adsorption. *Colloids Surf B Biointerfaces*. 2000, 18: 301–313.
 47. Aliabadi HM, Shahin M, Brocks DR, Lavasanifar A. Disposition of drugs in block copolymer micelle delivery systems: from discovery to recovery. *Clin Pharmacokinet*. 2008, 7: 619–634.
 48. Kim TY, Kim DW, Chung JY, Shin SG, Kim SC, et al. Phase I and pharmacokinetic study of Genexol-PM, a Cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. *Clin Cancer Res*. 2004, 10: 3708–3716.
 49. Hamaguchi T, Kato K, Yasui H, Morizane C, Ikeda M et al. A phase I and pharmacokinetic study of NK105, a paclitaxel-incorporating micellar nanoparticle formulation. *Br J Cancer*. 97: 170–176.
 50. Uchino H, Matsumura Y, Negishi T, Koizumi F, Hayashi T et al. Cisplatin-incorporating polymeric micelles (NC-6004) can reduce nephrotoxicity and neurotoxicity of cisplatin in rats. *Br J Cancer*. 2005, 93: 678–687.
 51. Matsumura Y, Hamaguchi T, Ura T, Muro K, Yamada Y et al. Phase I clinical trial and pharmacokinetic evaluation of NK911, a micelle-encapsulated doxorubicin. *Br J Cancer*. 2004, 91: 1775–1781.
 52. Lee CC, MacKay JA, Frechet JM, Szoka FC. Designing dendrimers for biological applications. *Nat Biotechnol*. 2005, 23: 1517–1526.
 53. Quintana A, Raczka E, Piehler L, Lee I, Myc A et al. Design and function of a dendrimer-based therapeutic nanodevice targeted to tumor cells through the folate receptor. *Pharm Res*. 2002, 19: 1310–1316.
 54. Gradishar WJ. Albumin-bound paclitaxel: a next-gener-

- ation taxane. *Expert Opin Pharmacother*. 2006, 7: 1041–1053.
55. Adler HI, Fisher WD, Cohen A, Hardigree AA. Miniature *Escherichia coli* cells deficient in DNA. *Proc Natl Acad Sci USA*. 1967, 57: 321–326.
56. Paciotti GF, Myer L, Weinreich D, Goia D, Pavel N et al. Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. *Drug Deliv*. 2004, 11: 169–183.
57. Reiter C, CapciKaragoz A, Frohlich T. Synthesis and study of cytotoxic activity of 1,2,4-trioxane- and egonol-derived hybrid molecules against *Plasmodium falciparum* and multidrug-resistant human leukemia cells. *Eur J Med Chem*. 2014, 75: 403–412.
58. Sasaki Y, Oshima Y, Koyama R. A novel approach to cancer treatment using structural hybrids of the p53 gene family. *Cancer Gene Ther*. 2012, 19: 749–756.
59. Okuhira K, Demizu Y, Hattori T. Development of hybrid small molecules that induce degradation of estrogen receptor-alpha and necrotic cell death in breast cancer cells. *Cancer Sci*. 2013, 104: 1492–1498.
60. Kawamoto M, Horibe T, Kohno M. HER2-targeted hybrid peptide that blocks HER2 tyrosine kinase disintegrates cancer cell membrane and inhibits tumor growth in vivo. *Mol Cancer Ther*. 2013, 12: 384–393.
61. Nair BP, Vaikkath D, Nair PD. Polyhedraloligomeric silsesquioxane-F68 hybrid vesicles for folate receptor targeted anti-cancer drug delivery. *Langmuir*. 2014, 30: 340–347.
62. Poveda A, Lopez-Pousa A, Martin J. Phase II Clinical Trial With Pegylated Liposomal Doxorubicin (CAELYX(R)/Doxil(R)) and Quality of Life Evaluation (EORTC QLQ-C30) in Adult Patients With Advanced Soft Tissue Sarcomas: A study of the Spanish Group for Research in Sarcomas (GEIS). *Sarcoma*. 2005, 9: 127–132.
63. O'Brien ME, Wigler N, Inbar M, CAELYX Breast Cancer Study Group. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol*. 2004, 15(3): 440–449.
64. Shiah JG, Sun Y, Peterson CM. Antitumor activity of N-(2-hydroxypropyl) methacrylamide copolymer-Mesochlorine e6 and adriamycin conjugates in combination treatments. *Clin Cancer Res*. 2000, 6: 1008–1015.
65. Vasey P. Phase I clinical and pharmacokinetic study of PK1 (HPMA copolymer doxorubicin) first member of a new class of chemotherapeutics agents: drug-polymer conjugates. *Clin. Cancer Res*. 1999, 5: 83–94.
66. Thomson AH. Population pharmacokinetics in phase I drug development: a phase I study of PK1 in patients with solid tumours. *Br J Cancer*. 1999, 81: 99–107.
67. Cassidy J. PK1: Results of Phase I studies. *Proc 5th Intl Symp on Polymer Therapeutics: From Laboratory to Clinical Practice*, Cardiff, UK 20. 2000.
68. Kim DW, Kim SY, Kim HK, Kim SW, Shin SW et al. Multicenter phase II trial of Genexol-PM, a novel Cremophor-free, polymeric micelle formulation of paclitaxel, with cisplatin in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2007, 18: 2009–2014.
69. Leng ZH, Zhuang QF, Li YC. Polyamidoamine dendrimer conjugated chitosan nanoparticles for the delivery of methotrexate. *Carbohydr Polym*. 2013, 98: 1173–1178.
70. Gupta N, Hatoum H, Dy GK. First line treatment of advanced non-small-cell lung cancer - specific focus on albumin bound paclitaxel. *Int J Nanomedicine*. 2014, 9: 209–221.