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Drug Delivery in Cancer - Technologies, Markets and Companies

Description: Drug delivery remains a challenge in management of cancer. Approximately 12.5 million new cases of cancer are being diagnosed worldwide each year and considerable research is in progress for drug discovery for cancer. Cancer drug delivery is no longer simply wrapping up cancer drugs in a new formulations for different routes of delivery. The focus is on targeted cancer therapy. The newer approaches to cancer treatment not only supplement the conventional chemotherapy and radiotherapy but also prevent damage to normal tissues and prevent drug resistance.

Innovative cancer therapies are based on current concepts of molecular biology of cancer. These include antiangiogenic agents, immunotherapy, bacterial agents, viral oncolysis, targeting of cyclic-dependent kinases and tyrosine kinase receptors, antisense approaches, gene therapy and combination of various methods. Important methods of immunotherapy in cancer involve use of cytokines, monoclonal antibodies, cancer vaccines and immunogene therapy.

Several innovative methods of drug delivery are used in cancer. These include use of microparticles as carriers of anticancer agents. These may be injected into the arterial circulation and guided to the tumor by magnetic field for targeted drug delivery. Polyethylene glycol (PEG) technology has been used to overcome some of the barriers to anticancer drug delivery. Encapsulating anticancer drugs in liposomes enables targeted drug delivery to tumor tissues and prevents damage to the normal surrounding tissues. Monoclonal antibodies can be used for the delivery of anticancer payloads such as radionucleotides, toxins and chemotherapeutic agents to the tumors.

Antisense oligonucleotides have been in clinical trials for cancer for some time now. RNAi has also been applied in oncology. Small interfering RNAs (siRNAs) can be targeted to tumors and one example is suppression of H-ras gene expression indicating the potential for application in therapy of ovarian cancer. Cancer gene therapy is a sophisticated form of drug delivery for cancer. Various technologies and companies developing them are described. Nucleic acid-based cancer vaccines are also described.

Drug delivery strategies vary according to the type and location of cancer. Role of drug delivery in the management of cancers of the brain, the bladder, the breast, the ovaries and the prostate are used as examples to illustrate different approaches both experimental and clinical. Biodegradable implants of carmustine are already used in the treatment of malignant brain tumors.

The market value of drug delivery technologies and the anticancer drugs are difficult to separate. Cancer market estimates from 2008-2018 are given according to organs involved and the types of cancer as well as according to technologies. Distribution of the into major regions is also described.

Profiles of 205 companies involved in developing innovative cancer therapies and methods of delivery are presented along with their 221 collaborations. The bibliography contains over 600 publications that are cited in the report. The report is supplemented with 55 tables and 8 figures.

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2. Innovative treatments for cancer

Introduction

Selective estrogen receptor modulators Antiangiogenic strategies for cancer Development of antiangiogenic therapies Classification of antiangiogenic agents Examples of antiangiogenic agents Chemotherapy at lower than maximum tolerated dose Inhibitors of endothelial proliferation Inducers of apoptosis of endothelial cells of tumor vessels Lodamin Matrix metalloproteinase inhibitors Monoclonal antibodies with vasculostatic properties PPARa agonists Rapalogues as antiangiogenic agents VEGF Trap Agents that decrease the permeability of tumor blood vessels Antiangiogenic agents in clinical trials Combination of antiangiogenic with cytotoxic therapy Bacterial anticancer agents Tumor-targeted bacteria Genetically modified Salmonella typhimurium as anticancer agent TAPET (Tumor Amplified Protein Expression Therapy) Bacterial protein for targeted delivery of liposomal cancer drugs Killed but metabolically active (KBMA) bacteria Bacterial toxins targeted to tumors Immunotoxins Escherichia Coli toxins Engineered anthrax toxin Recombinant fusion toxins Type III secretion systems Induction of apoptosis in cancer by bacterial proteins Induction of immune response by bacteriolytic therapy

Innovations in cell therapy for cancer Stem cell transplantation for cancer Cancer drug/gene delivery by mesenchymal stem cells Cancer immunotherapy Cytokines Cancer vaccines 5T4 as a target for cancer immunotherapy Anti-telomerase vaccine Antigen-specific cancer vaccines Carcinoembryonic antigen-based vaccines Dendritic cells for cancer vaccination Hybrid cell vaccination Lymphocyte-based cancer therapies Tumor cell vaccines Vaccines that simultaneously target different cancer antigens Concluding remarks about cancer vaccines Cancer Vaccine Consortium Innovative methods of radiation delivery Image-guided ultrasound technology for delivery of radiation Respiratory gating technology for radiation therapy Positron therapy Boron neutron capture therapy Application of drug delivery systems to BNCP Use of nanotechnology to enhance BNCT Skeletal Targeted Radiotherapy Irreversible electroporation Methods to overcome multidrug resistance (MDR) P-glycoprotein-mediated MDR MDR-associated protein gene Strategies for overcoming MDR Blocking the action of P-glycoprotein Nitric oxide inducers Managing resistance to antiapoptotic action of anticancer agents Inhibition of DNA repair Liposome formulation of drugs Modification of the chemical structure of the anticancer drug Enzyme Catalyzed Therapeutic Activation Modulation of SPARC expression Iron chelators that overcomes resistance to chemotherapeutics Proton pump inhibitors Combination of targeted drugs with different specificities Targeted cancer therapies Targeting cellular pathways Targeting antigens in virus-associated cancer Targeting HAAH for cancer therapy Targeting mitochondrial membranes Targeting tumor lymphatics Targeting tyrosine kinase receptors Inhibitors of bcr-abl tyrosine kinase Inhibition of multiple tyrosine kinases Inhibitors of ErbB tyrosine kinase Targeting the Hedgehog signaling pathway Targeting caspase-8 Targeting oncogenes Targeting miRNA for cancer therapeutics Targeting the transferrin receptor-mediated endocytosis pathway Targeted anticancer therapies based on the Rad51 promoter Targeting cancer stem cells Targeting glycoproteins Tagging cancer with sugars Anticancer agents based on glycobiology Targeting cell surface glycoproteins Biofusion for targeted cancer therapy

Targeted drug delivery of anticancer agents with controlled activation Targeted delivery of anticancer agents with ReCODE[™] technology Enhancing the effects of radiation and chemotherapy Sensitizing agents for chemotherapy Tesmilifene for chemosensitization CoFactor to enhance the efficacy of chemotherapy Enzyme-enhanced chemotherapy Sensitizing agents for radiotherapy IPdR Manipulation of tumor oxygenation Hypoxia-based methods to enhance chemotherapy and radiotherapy Hyperbaric oxygen and radiation HIF-1 antagonists to enhance radiotherapy Nonsteroidal antiinflammatory drugs enhance tumor radiosensitivity ONCONASE as radiosensitivity enhancer Hyperthermia and chemotherapy/radiation therapy Techniques for hyperthermia Trimodality therapy: radiation, chemotherapy, and hyperthermia Photodynamic therapy Novel anticancer agents Anti-EphA2 antibodies Antioxidants Brostallicin Agents disrupting folate metabolism Pemetrexed Cell cycle inhibitors Cytotoxic ribonucleases DNA hypomethylating agents Histone-based cancer therapy Histone deacetylase inhibitors Modulation of p300/CBP histone acetyltransferase activity Simulation of endogenous histone for anticancer therapy HSP90 inhibitors Ion channel blockers IOT-101 Endovion LPAAT-beta inhibitors P13-kinase inhibitors PARP inhibitors Targeted destruction of BRCA2 deficient tumors by PARP inhibitors Prodruas Enzyme-activated prodrugs Ascorbic acid as a prodrug for cancer Prolarix Protein kinase G activation Proteasome inhibitors Recombinant human insulin-like growth factor binding protein-3 Second generation nucleosides Targeting topoisomerase IB Telomerase inhibitors Therapeutic strategies based on the P53 pathway Therapeutic strategies based on molecular mechanisms In vivo models for molecularly anticancer drugs Checkpoint activation as a strategy against cancer Deletion-specific targeting for cancer therapy Repair-blocking drugs for enhancing effect of chemotherapy Combining novel anticancer approaches Personalized therapy of cancer Challenges of cancer classification Design of future cancer therapies Personalized drug development in oncology Role of molecular imaging Role of molecular imaging in targeted cancer therapy

Screening for personalized anticancer drugs Targeting pathways for personalized cancer therapy

3. Drug delivery systems for cancer

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Nanoparticles containing albumin and antisense oligonucleotides Non-aggregating nanoparticles Pegylated nanoliposomal formulation Perfluorocarbon nanoparticles Protosphere nanoparticle technology Nanoparticles for targeted delivery of drugs into the cancer cells Antiangiogenic therapy using nanoparticles Carbon magnetic nanoparticles for targeted drug delivery in cancer Carbon nanotubes for targeted drug delivery to cancer cells Fullerenes for enhancing tumor targeting by antibodies Gold nanoparticles for drug delivery in cancer Iron oxide magnetic nanoparticle formulation for drug delivery Lipoprotein nanoparticles targeted to cancer-associated receptors Magnetic nanoparticles for remote-controlled drug delivery to tumors Nanobees for targeted delivery of cytolytic peptide melittin Nanocell for targeted drug delivery to tumor Nanodroplets for site-specific cancer treatment Phage nanoparticles as antibody-drug conjugates Polymer nanoparticles for targeted drug delivery in cancer Polymersomes for targeted cancer drug delivery Targeted drug delivery with nanoparticle-aptamer bioconjugates Dendrimers for anticancer drug delivery Application of dendrimers in boron neutron capture therapy Application of dendrimers in photodynamic therapy Dendrimer-based synthetic vector for targeted cancer gene therapy Devices for nanotechnology-based cancer therapy Convection-enhanced delivery with nanoliposomal CPT-11 Nanocomposite devices Nanoengineered silicon for brachytherapy Nanoparticles combined with physical agents for tumor ablation Carbon nanotubes for laser-induced cancer destruction Nanoparticles and thermal ablation Nanoparticles combined with ultrasound radiation of tumors Nanoparticles as adjuncts to photodynamic therapy of cancer Nanoparticles for boron neutron capture therapy RNA nanotechnology for delivery of cancer therapeutics Nanocarriers for simultaneous delivery of multiple anticancer agents Combination of diagnostics and therapeutics for cancer Biomimetic nanoparticles targeted to tumors Dendrimer nanoparticles for targeting and imaging tumors Gold nanorods for diagnosis plus photothermal therapy of cancer Magnetic nanoparticles for imaging as well as therapy of cancer Nanobialys for combining MRI with delivery of anticancer agents pHLIP nanotechnology for detection and targeted therapy of cancer Radiolabeled carbon nanotubes for tumor imaging and targeting Targeted therapy with magnetic nanomaterials guided by antibodies Ultrasonic tumor imaging and targeted chemotherapy by nanobubbles Polyethylene glycol technology Enzon's PEG technology Debiopharm's PEG biconjugate drug delivery platform **Nektar PEGylation PEG Intron** Single-chain antibody-binding protein technology Vesicular systems for drug delivery in cancer Liposomes for anticancer drug delivery Antibody-targeted liposomes for cancer therapy AIZA's Stealth liposomes Boron-containing liposomes DepoFoam technology Hyperthermia and liposomal drug delivery Liposomal doxorubicin formulation with N-octanoyl-glucosylceramide Liposome-nucleic acid complexes for anticancer drug delivery Non-pegilated liposomal doxorubicin

Tumor-selective targeted drug delivery via folate-PEG liposomes Ultrasound-mediated anticancer drug release from liposomes Companies developing liposome-based anticancer drugs Pharmacosomes for controlled anticancer drug delivery Emulsion formulations of anticancer drugs Albumin-based drug carriers Anticancer drugs that bind to tumors Monoclonal antibodies Murine monoclonal antibodies Humanized MAbs Actions and uses of monoclonal antibodies in cancer Targeted antibody-based cancer therapy Antibody-cytokine fusion proteins Antibody J591 for targeted delivery of anticancer therapy Anti-Thomsen-Friedenreich antigen MAb Combining MAbs with anti-CD55 antibody MAbs targeted to alpha fetaprotein receptor MAbs targeted to tumor blood vessels MAbs targeted to HAAH MAbs for immune activation Delivery of cancer therapy with MAbs Antibody-directed enzyme prodrug therapy Chemically programmed antibodies Combining diagnostics with therapeutics based on MAbs Radiolabeled antibodies Clinical development of MAbs for treatment of cancer Advantages and limitations of MAbs for cancer therapy Monoclonal T cell receptors Radioactive materials for diagnosis and targeted therapy of cancer Theophylline enhances radioiodide uptake by cancer Radiolabeled somatostatin receptor antagonists Strategies for drug delivery in cancer Direct introduction of anticancer drugs into the tumor Injection into the tumor Antineoplastic drug implants into tumors Tumor necrosis therapy Injection into the arterial blood supply of cancer Electrochemotherapy Pressure-induced filtration of drugs across vessels to the tumor Improving drug transport to tumors Carbohydrate-enhanced chemotherapy Dextrans as macromolecular anticancer drug carriers In situ production of anticancer agents in tumors Targeted drug delivery in cancer Affibody molecules for targeted anticancer therapy Fatty acids as targeting vectors Genetic targeting of the kinase activity in cancer cells Heat-activated targeted drug delivery Novel transporters to target photosensitizers to cancer cell nuclei Photodynamic therapy of cancer Radionuclides delivered with receptor targeting technology Targeting ligands specific for cancer cells Targeting abnormal DNA in cancer cells Targeting using a bispecific antibody Targeted chemotherapy using transporters Targeted generation of intracellular reactive oxygen species Targeted cytotoxic peptides Targeted delivery to receptors found in tumors Targeted delivery by tumor-activated prodrug therapy Targeting glutathione S-transferase Targeting tumors by exploiting leaky blood vessels Transmembrane Carrier Systems Transferrin-oligomers as targeting carriers in anticancer drug delivery

Ultrasound and microbubbles for targeted anticancer drug delivery Ultrasound for targeted delivery of chemotherapeutics Vitamin B12 and folate for targeting cancer chemotherapy Drug delivery in relation to circadian rhythms Implants for systemic delivery of anticancer drugs Drug-eluting polymer implants Angiogenesis and drug delivery to tumors Antiangiogenesis strategies Targeting tumor endothelial cells Methods for overcoming limitations of antiangiogenesis approaches Vascular targeting agents Alpha-emitting antibodies for vascular targeting Angiolytic therapy Anti-phosphatidylserine antibodies as VTA AS1404 Cadherin inhibitors Combretastatin A4 Prodrug Drugs to induce clotting in tumor vessels Selective permeation of the anticancer agent into the tumor Targeted delivery of tissue factor Vascular targeting agents versus antiangiogenesis agents ZD6126 Delivery of proteins and peptides for cancer therapy CELLECTRA[™] electroporation device Emisphere's eligen[™] system Diatos Peptide Vector intra-cellular/intra-nuclear delivery technology Lytic peptides and cancer Modification of proteins and peptides with polymers Peptide-based targeting of cancer biomarkers for drug delivery Peptide-cytokine complexes as vascular targeting agents Peptide-polymer conjugates with radionuclides Transduction of proteins in vivo Tumor targeting by stable toxin (ST) peptides Cell-based cancer vaccines Autologous tumor cell vaccines Vaccines that simultaneously target different cancer antigens Delivery systems for cancer vaccines A computational approach to integration of drug delivery methods for cancer

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Aptamers for combined diagnosis and therapeutics of cancer Antisense compounds in clinical trials **RNA** interference Basics of RNAi Comparison of antisense and RNAi RNAi applications in oncology Delivery of siRNA by nanoparticles Delivery of siRNA by nanosize liposomes Lipid nanoparticles for delivery of anticancer siRNAs Polymer nanoparticles for targeted delivery of anticancer siRNA Companies developing cancer therapies based on antisense and RNAi **DNA** interference Cancer gene therapy Basics of gene therapy Strategies for cancer gene therapy Gene transfer techniques as applied to cancer gene therapy Viral vectors Non-viral vectors A polymer approach to gene therapy for cancer Direct gene delivery to the tumor Injection into tumor Reversible electroporation Hematopoietic gene transfer Genetic modification of human hematopoietic stem cells Gene-based strategies for immunotherapy of cancer (immunogene therapy) Cytokine gene therapy Monoclonal antibody gene transfer Transfer and expression of intracellular adhesion-1 molecules Other gene-based techniques of immunotherapy of cancer Fas (Apo-1) Chemokines Major Histocompatibility Complex (MHC) Class I IGF (Insulin-Like Growth Factor) Inhibition of immunosuppressive function Delivery of toxic genes to tumor cells for eradication (molecular chemotherapy) Gene-directed enzyme prodrug therapy Combination of gene therapy with radiotherapy Multipronged therapy of cancer with microencapsulated cells Correction of genetic defects in cancer cells (mutation compensation) Targeted gene therapy for cancer Transcriptional targeting for cancer gene therapy Targeted epidermal growth factor-mediated DNA delivery Gene-based targeted drug delivery to tumors Targeting gene expression to hypoxic tumor cells Targeting gene expression by progression-elevated gene-3 promoter Targeted delivery of retroviral particles hitchhiking on T cells Targeting tumors with genetically modified T cells Targeting tumors by genetically engineered stem cells Tumor-targeted gene therapy by receptor-mediated endocytosis Targeted site-specific delivery of anticancer genes by nanoparticles Immunolipoplex for delivery of p53 gene Combination of electrogene and electrochemotherapy Virus-mediated oncolysis Targeted cancer treatments based on oncolytic viruses Oncolytic gene therapy Cytokine-induced killer cells for delivery of an oncolytic virus Facilitating oncolysis by targeting innate antiviral response by HDIs **Oncolytic HSV** Oncolytic adenoviruses Oncolytic Coxsackie virus A21 Oncolytic vesicular stomatitis virus Oncolytic measles virus Oncolytic paramyxovirus

Oncolvtic reovirus Oncolytic vaccinia virus Cancer terminator virus Monitoring of viral-mediated oncolysis by PET Companies developing oncolytic viruses Bacteria as novel anticancer gene vectors Apoptotic approach to improve cancer gene therapy Concluding remarks on cancer gene therapy Cancer gene therapy companies Cell therapy for cancer Cellular immunotherapy for cancer Treatments for cancer by ex vivo mobilization of immune cells Granulocytes as anticancer agents Neutrophil granulocytes in antibody-based immunotherapy of cancer Use of hematopoietic stem cells for targeted cancer therapy Cancer vaccines Nucleic acid-based cancer vaccines DNA cancer vaccines Methods of delivery of DNA vaccines **RNA** vaccines Viral vector-based cancer vaccines Companies involved in nucleic acid-based vaccines Genetically modified cancer cells vaccines GVAX cancer vaccines Genetically modified dendritic cells Multipeptide-based cancer vaccines

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BBB disruption Nanoparticle-based targeted delivery of chemotherapy across the BBB Tyrosine kinase inhibitor increases topotecan penetration into CNS Intra-arterial chemotherapy Interstitial delivery of dexamethasone for reduction of peritumor edema Photodynamic therapy for chemosensitization of brain tumors Nanoparticles for photodynamic therapy of brain tumors Innovative delivery of radiotherapy to brain tumors GliaSite Radiation Therapy System Boron neutron capture therapy for brain tumors Cell therapy for glioblastoma multiforme Mesenchymal stem cells to deliver treatment for gliomas Gene therapy for glioblastoma multiforme Single-chain antibody-targeted adenoviral vectors Intravenous gene delivery with nanoparticles into brain tumors Neural stem cells for drug/gene delivery to brain tumors Peptides targeted to glial tumor cells Targeting normal brain cells with an AAV vector encoding interferon-b Treatment of medulloblastoma by suppressing genes in Shh pathway Antiangiogenic gene therapy Anticancer drug delivery by genetically engineered MSCs RNAi gene therapy of brain cancer Ligand-directed delivery of dsRNA molecules targeted to EGFR Virus-mediated oncolytic therapy of brain cancer Vaccination for glioblastoma multiforme Breast Cancer Combination targeted treatment stops breast cancer growth Therapies for breast cancer involving innovative methods of drug delivery Injectable biodegradable polymer delivery system for local chemotherapy MammoSite brachytherapy Monoclonal antibodies for breast cancer Breast cancer vaccines HER-2 DNA AutoVacÔ vaccine Recombinant adenoviral ErbB-2/neu vaccine Gene vaccine for breast cancer NeuVax Gene therapy for breast cancer Intratumoral injection of Ad5CMV-p53 Antisense therapy for breast cancer Inhibitors of growth factors FGF2 and VEGF Drug delivery for cancer of the cervix and the uterus Gene therapy for cervical cancer Delivery of chemoradiation therapy Cervical cancer vaccines Leukemia Clofarabine Malignant melanoma Targeted therapies for melanoma Immunotherapy for malignant melanoma Gene therapy for malignant melanoma Neuroblastoma Genetically modified NSCs for treatment of neuroblastoma Non-small cell lung cancer Intratumoral administration of anticancer drugs through a bronchoscope Aerosol delivery of anticancer agents for lung cancer Aerosol gene delivery for lung cancer Ovarian cancer Innovative drug delivery for ovarian cancer Intraperitoneal delivery Gene Therapy for ovarian cancer Pancreatic cancer Targeted chemotherapy for pancreatic cancer Local anticancer drug delivery for pancreatic cancer

Vaccine for pancreatic cancer Gene therapy for pancreatic cancer Adenovirus-mediated transfer of vasostatin gene Rexin-GÔ for targeted gene delivery in pancreatic cancer Targeted Expression of BikDD gene Prostate cancer PACLIMER Microspheres PRX302 Brachytherapy for cancer of prostate Capridine-beta LHRH for prostate cancer LHRH analogs Histrelin implant Immunomodulatory drugs MAbs for prostate cancer Targeted therapies for prostate cancer Delivery of cisplatin to prostate cancer by nanoparticles Delivery of siRNAs to prostate cancer with aptamer-siRNA chimeras Delivery of siRNA for prostate cancer with metastases Nanoparticulate delivery of suicide DNA to prostate tumors PSA-activated protoxin that kills prostate cancer Targeted drug delivery with nanoparticle-aptamer bioconjugates Targeting oncogene MDM2 in prostate cancer Vascular targeting of prostate cancer Gene therapy for cancer of prostate Experimental studies Tumor suppressor gene therapy in prostate cancer Clinical trials Combined approaches Combined autovaccination and hyperthermia Hepatocellular carcinoma

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