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"REVIEW ON- CANCER TARGETING DRUG DELIVERY SYSTEM"

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ABSTRACT

Advancement in science and technology has brought a motivating modification in medical aid of cancer. Particles square measure built in such the way so they're drawn to unhealthy cells, which permit direct treatment of cancer cells. Drug delivery systems management the situation within the body wherever it is discharged and also the rate at that a drug is discharged. standard therapy possesses some serious aspect effects, together with harm of the system and alternative numerous varieties of organs with speedily proliferating cells thanks to non-specific targeting, lack of solubility, and inability to enter the core a part of the growth which ends up in impaired treatment with the reduced dose and low survival rate. Nanoparticles will be programmed in such the way so it will recognize the cancerous cells by giving selective and correct drug delivery avoiding interaction with the healthy cells. the most aim of this review focuses on numerous methods for neoplastic cell targeting. It additionally discusses specific drug delivery by nanoparticles within the cells, illustrating many booming researches within the field of cancer medical aid.

Keywords: *Cancer, engineering science, Targeted delivery, Therapy, Recent advances*

1. INTRODUCTION

Cancer remains one of the leading causes of death in most parts of the world:

1. Early prognosis of the disease due to regular screening and better understanding of the path physiology of tumor progression has opened many new vistas as therapy options. In most solid tumors, after its surgical removal, the remaining cancer cells are managed with a variety of treatment options including, radiotherapy, chemotherapy, immunotherapy, etcetera

2. However, once the cancer is metastasized, the treatment options are limited, and chemotherapy remains the choice of treatment. The main reason for failure of chemotherapy is the poor accessibility of antineoplasticagents to the tumor, requiring higher doses, and the nonselective nature of these agents causes severe toxicity

3. Thus, targeted drug delivery holds immense potential to improve the treatment of cancer by selectively providing therapeutically effective drug concentrations at the tumor site. This review is an attempt to present an overview of the problems related to targeted drugdelivery in cancer, and to provide an insight into the issues related to the development of targeted drug delivery systems for cancer. Targeted drug delivery, sometimes called smart drug delivery,

4. Is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others? This means of delivery is largely founded on nanomedicine, which plans to employ nanoparticle-mediated drug delivery in order to combatthe downfalls of conventional drug delivery. These nanoparticles would be loaded with drugs and targeted to specific parts of the body where there is ely diseased tissue, thereby avoiding interaction with healthy tissue.The goal of a targeted drug delivery system is to prolong, localize, target and have protected drug interaction with the diseased tissue. The conventional drug delivery system is the absorption of the drug across a biological membrane, whereas the targeted release system releases the drug in a dosage form. The advantages to the targeted release system is the reduction in the frequency of the dosages taken by the patient, having a more uniform effect of the drug, reduction of drug side-effects, and reduced fluctuation in circulating drug levels. The disadvantage of the system is high cost, which makes productivity more difficult and the reduced ability to adjust the dosages.Targeted drug delivery systems have been developed to optimize regenerative techniques. The system is based on a method that delivers a certain amount of a therapeutic agent for a prolonged period of time to a targeted diseased area within the body.

2. NEED FOR TARGETED DRUG DELIVERY SYSTEMS

The quest for specificity of therapeutic agents is implicit all treatment modalities. In cancer treatment, wherever therapy and radio therapeutic choices are designed to kill cells, the specificity of drug action gains preponderating importance. These ways ar supported the basic principle of preferentially killing cancer cells, while not having any important noxious impact on traditional cells. it's necessary that everyone the cancer cells should be killed, either directly as a result of drug impact or indirectly thanks to witness impact of the medical care so as to realize a complete remission in patients presenting a disseminated disease therapy regimens alone are not entirely satisfactory in aggressive carcinomas and infrequently manufacture solely transient responses. Combination medical care, that involves high dose of radiation with continuous infusion of chemotherapeutic agents (like paclitaxel) has been investigated for the management of unrespectable domestically advanced tumors ten . Paclitaxel radiosensitizes tumour cells, and thus the combination medical care is more practical than drug or radiation alone. Also, achieving therapeutically relevant drug concentrations within the tumour mass, particularly just in case of solid tumors for a time comfortable to permit therapeutic activity of the drug may be a major drawback. Poor penetrability of those medication into the biologically heterogeneous tumour mass ends up in residual tumor cells even when prolonged treatment with these cytotoxic agents three. High dose therapy needed to take care of a state of complete remission causes intolerable systemic adverse effects, forcing the termination of medical care in several patients. Most of those adverse effects impose important compromises on the standard of life of patients. Thus, the low therapeutic indices of those treatment choices have resulted in a very rummage around for efficient delivery systems for the presently accessible medication, which may change maximizing the therapeutic effectuality of the medication with stripped-down adverse effects. Targeting medication with specially designed drug delivery systems offers a profitable choice to enhance the therapeutic effectuality andto reduces the event of general toxicity of anti-cancer agents. Thus, the requirement for developing specifically targeted drug delivery systems arises from not solely the clinical perspective however will also facilitate in eradicating cancer from the patient before it kills the patient.

3. CELLULAR BARRIERS

The emergence of multi-drug resistance in growth cells because of the expression of drug-efflux proteins on cell surface has raised considerations concerning long run treatment with the chemotherapeutic agents eleven. Delivering the cytotoxicdrugs into the growth cells, prepacked in drug delivery systems will overcome the issues associated with multi-drug resistance (MDR) twelve. many mechanisms are planned for drug resistance. The membrane-bound p-glycoprotein (Pgp)-mediated flow mechanism is understood to reduce the intracellular accumulation of antitumor agents in most resistant cells13. what is more, some of the antitumor medicine square measure sequestered into the cytoplasmatic vesicles and extruded out, preventing their effective cytoplasmatic delivery or localization into the nucleus, the positioning of action of sure antitumor agents (e.g., antibiotic drug, cisplatin, et cetera) fourteen. another antitumor agents (e.g., doxorubicin) also are the substrates of the membrane-associated multi-drug resistance proteins (MRPs), that cut back their intracellular accumulation15. Various drug delivery approaches like polymerdrug conjugates16, nano and microparticles17, liposomes, and compound micellar systems18 square measure being investigated to beat the matter of drug resistance in cancer therapy19, 20.Although the on top of systems may improve the intracellular delivery of therapy agents as compared thereto with drug in resolution, they are doing not target drug on to the nucleus.Drug transport to the nucleus with the on top of delivery systems is generally keen about thepassive diffusion of free drug from the protoplasm to the nucleus, that may well be inefficient. Thisis because, besides the semipermeable membrane, P-gp has been shown to specific on intracellular organelles like the Golgi complex and also the nuclear membrane cover. Clacabrini et al. 21 have shown the presence of P-gp on the nuclear membrane of multidrug resistant variants whereas another study has incontestable the flow of antibiotic drug from the nucleus, therefore reducing the out there drug within the nucleus for desoxyribonucleic acid intercalation22. Thus, P-gp on the nuclear membrane envelope represents an additional defense that's developed by resistant cells against antineoplastic agents. Therefore, merely delivering the drug into the cytoplasmic compartment might not overcome the matter of drug resistance unless there's greater drug localization within the nucleus. Further, the effectualness of a number of the presently used drug delivery systems may well be restricted because they continue to be treed within the endo-lysosomal vesicles upon intracellular internalization23. Based on our recent studies with transferrin-conjugated nanoparticles, it seems that the length of drug retention in cancer cells, particularly in resistant cell line is crucial to beat the problem of drug resistance24. Therefore, sustained unleash formulations could also be more practical in anticancer medical care than different drug delivery mechanisms. Thus, understanding the mechanism of drug resistance is critically vital in developing effective drug delivery stratergy.

TARGETING IN CANCER medical aid PASSIVE TARGETING

- EPR result
- LOCALIZED DELIVERY ACTIVE TARGETING
- ANTIBODIES
- LIPOSOMES
- APTAMERS PASSIVE TARGETING

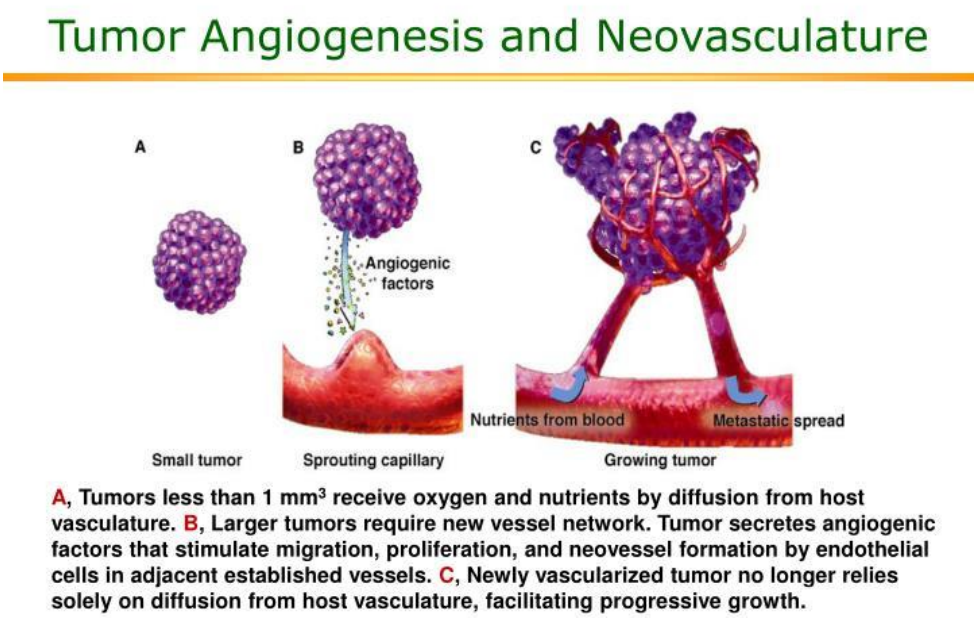
In passive targeting, the drug's success is directly associated with circulation time.25 This is achieved by cloaking the nanoparticle with some kind of coating. many substances are able to do this, with one in all them being synthetic resin glycol (PEG). By adding PEG to the surface of the nanoparticle, it's rendered deliquescent, therefore permitting water molecules to bind to the chemical element molecules on PEG via atomic number 1 bonding. The results of this bond could be a film of association round the nanoparticle that makes the substance antiphagocytic. The particles get this property thanks to the hydrophobic interactions that area unit natural to the RES (RES), therefore the drug-loaded nanoparticle is ready to stay in circulation for a extended amount of your time.26 to figure in conjunction with this mechanism of passive targeting, nanoparticles that area unit between ten and a hundred nanometers in size have been found to flow into systemically for extended periods of your time.27 EPR (ENHANCED porousness AND RETENTION) result The enhanced porousness and retention (EPR) result could be a idea by that molecules of certain sizes (typically liposomes, nanoparticles, and molecule drugs) tend to accumulate in neoplasm tissue rather more than they are doing in traditional tissues.28 the final

rationalization that's given for this development is that, so as for neoplasm cells to grow quickly, they need to stimulate the production of blood vessels. VEGF and alternative growth factors area unit concerned in cancer ontogenesis TARGETING IN CANCER medical aid PASSIVE
Tumor cell aggregates as little as 150–200 μm, begin to become hooked in to blood offer

carried out by neovasculature for his or her nutritionary and element offer.These fresh shaped neoplasm vessels square measure typically abnormal in kind and design. They are poorly aligned defective epithelium cells with wide fenestrations, lacking a sleek muscle layer, or innervation with a wider lumen, and impaired useful receptors for Hypertensin. Furthermore, neoplasm tissues typically lack effective humor evacuation. All of those factors cause abnormal molecular and fluid transport dynamics, particularly for organic compound medication. This phenomenon is noted because the "enhanced permeableness and retention (EPR) effect" of macromolecules and lipids in solid tumors. The EPR impact is additional increased by several pathophysiological factors concerned in enhancement of the extravasation of macromolecules in solid neoplasm tissues. For instance, bradykinin, gas / peroxynitrite, prostaglandins, tube permeableness issue (also referred to as tube epithelium protein VEGF), neoplasm mortification issue et al.. One factor that ends up in the accumulated retention is that the lack of lymphatics round the neoplasm region which would separate such particles underneath traditional conditions.

GROWTH OF A TUMOR

The EPR impact is typically used to explain nanoparticle and vesicle delivery to cancer tissue. 29 one in every of several examples is that the work



A, Tumors less than 1 mm³ receive oxygen and nutrients by diffusion from host vasculature. B, Larger tumors require new vessel network. Tumor secretes angiogenic factors that stimulate migration, proliferation, and neovessel formation by endothelial cells in adjacent established vessels. C, Newly vascularized tumor no longer relies solely on diffusion from host vasculature, facilitating progressive growth.

relating to thermal ablation with gold nanoparticles. Halas, West and coworkers have shown a attainable complement to radiation and therapy in cancer medical care, whereby once nanoparticles square measure at the cancer website they will be hot in response to a skin penetrating close to IR optical maser (Photothermal effect). This medical care has shown to work best in conjunction with chemotherapeutics or different cancer therapies.30 though the EPR effect has been postulated to hold the nanoparticles and unfold within the cancer tissue.

4. DRUG CARRIER SYSTEMS

1. NAKED ANTIBODIES
2. IMMUNOTOXINS
3. CHIMERIC PROTEINS
4. NANO SYSTEMS/DRUG CARRIERS
5. NAKED ANTIBODIES

Aptamers are a class of therapeutic oligonucleotides that form specific three-dimensional structures that are dictated by their sequences. In contrast to antisense oligonucleotides and small interfering RNAs (siRNAs) that inhibit translation of proteins by Watson-Crick base-pairing to their respective messenger RNAs, aptamers bind to existing proteins (and, less commonly, non-protein targets) with high affinity and specificity, analogous to monoclonal antibodies.Antibodies raised against the tumor associated antigens, which serve a critical function forcell growth can by themselves

function as a therapeutic option for tumor treatment. Examples include Herceptin® (Trastuzumab, Genentech) which is the antibody against Her-2, a tyrosine kinase found in breast cancer cells. Herceptin® isan unconjugated humanized monoclonal antibody against Her-2 and induces apoptosis in tumor cells, thus clinically useful against metastatic breast cancers over expressing Her-2. Avastin® (bevacizumab) is another monoclonal antibody targeted against vascular endothelial growth factor (VEGF) that is involved in angiogenesis in tumors. Avastin improves the overall survival in patients of colorectal cancer, when given in combination with standard chemotherapy. 46

IMMUNOTOXINS

Immunotoxins are the products of conjugation of whole monoclonal antibodies to bacterial or plant toxins, for example, pseudomonas exotoxin and diphtheria toxin. Non-specific toxicity due to these natural toxins can be eliminated by mutating or deleting the ability of the toxin to bind to its own receptor. Still these targeted toxins carry a high risk of non-specific toxicity to normal cells at higher doses.

CHIMERIC PROTEINS

These new and interesting targeted molecules recognize and specifically kill the tumor cells, which over express specif ic receptors. Chimeric proteins are chemical conjugates of some small cytokines, hormones, or growth factor based ligands with the natural toxins, such as pseudomonas exotoxin (PE) and diphtheria toxin47. Chimeric proteins constructed using a GnRH analog fused to PE, inhibited tumor formation by 80% in a nude-mouse colon adenocarcinoma xenograft model 48 . GnRH acts as the targeting moiety for adenocarcinoma cells, while PE kills.

NANOSYSTEMS/DRUG CARRIERS

Anti-cancer medicine are often related to the mixture drug carrier systems likepolymeric micelles, nanoparticles, and liposomes, which might then be actively targeted to specifictumor cells by suggests that of ligands or antibodies against growth associated cell surface receptors. This strategy of targeted drug delivery will overcome the cellular primarily based mechanisms of multi- rug resistance, and improves the property of drug delivery to the cancer cells50. Anticancer agents encapsulated in nanoparticles can't be recognized by the cellular efflux mechanisms and so circumvent the event of multi-drug resistance. Such nano-sized drug carriers ar capable of passively accumulating within the growth tissue victimization the EPR effect, once ready in acceptable sizes and with long current properties in blood stream. Also, surface modifications of the nanoparticles are often achieved which might permit specific biochemical interactions with the proteins/receptors expressed on growth cells. We have demonstrated magnified efficaciousness of paclitaxel-loaded nanoparticles on conjugation with transferrin, in an exceedingly murine model of prostate cancer24 Transferrin receptors ar overexpressed by 2-10 folds in growth cells than in traditional cellsand so beta globulin and/or beta globulin antibodies are used for targeting medicine to growth cells. Single-dose intratumoral injection of beta globulin conjugated paclitaxel nanoparticles produced a whole regression and a considerably higher survival rate than the unconjugated nanoparticles or drug dissolved in Cremophor EL in an exceedingly murine model of prostatic adenocarcinoma. Greater cellular uptake of drug victimization beta globulin conjugated nanoparticles was chargeable for the bigger efficacy of beta globulin conjugated nanoparticles.

5. CONCLUSION

Targeted drug delivery to tumors will increase the property for killing cancer cells, decrease the peripheral/systemic toxicity and might allow a dose increase. Advances in identification of growth specific targets and development of various drug delivery approaches for tumor targeting have raised hopes for the event of a roaring targeted drug delivery modality for cancer medical aid. although the final word aim is to eradicate cancer from the patient, more sensible goals aiming at up the standard of lifetime of patients ar on the brink of fruition. The next few years can witness specific stress on the event of systems that can not solely acknowledge specific targets on cancer cells however are also capable of expeditiously internalizing into the cells. Combination of targeting approaches could offer solutions to some of these issues. Further, utilizing specific molecular addresses on the tube-shaped structure epithelium, targeting victimisation magnetic fields, and ultrasound ar a number of the rising ideas that hold immense promise for drug targeting in cancer medical aid. of these would need higher understanding of the unwellness, identification of growth specific markers, and coincidingdevelopment of latest medication that ar stiffer and fewer nephrotoxic. for brand spanking new medication to create theirway into the clinic, the drug discovery project ought to run in conjunction with new drug deliverysystem development, so these medication don't fall prey to unfavorable pharmacological medicine andare discarded within the development pipeline itself. Targeting ways, involving engineering scienceand bioconjugation chemistry, which might alter a drug's misdistribution to avoid toxicity andmaximize its efficaciousness, will enhance the prospects of latest antineoplastic drugs reaching the patients.

REFERENCES

[1] Beardsley, T. A War not Won. Sci Am 270, 130-138 (1994).

[2] Jain, R. K. Delivery of Molecular and Cellular Medicine to Solid Tumors. Adv Drug Deliv Rev 46, 149-168 (2001).

[3] Jang, S. H., Wientjes, M. G., Lu, D., Au, J. L. Drug Delivery and Transport to Solid Tumors. Pharm Res 20, 1337-1350 (2003).

[4] Muller, R; Keck, C (2004). "Challenges and solutions for the delivery of biotech drugs – a review of drug nanocrystal technology and lipid nanoparticles". Journal of Biotechnology. 113 (1–3): 151–170.

[5] Saltzman, W. Mark; Torchilin, Vladimir P. (2008). "Drug delivery systems". AccessScience. McGraw-Hill Companies.

[6] Trafton, A. Tumors Targeted Using Tiny Gold Particles. MIT Tech Talk. 2009, 53, 4–4.

[7] Bertrand N, Leroux JC.; Leroux (2011). "The journey of a drug carrier in the body: an anatomo-physiological perspective". Journal of Controlled Release. 161 (2): 152–63.

[8] Scott, Robert C; Crabbe, Deborah; Krynska, Barbara; Ansari, Ramin; Kiani, Mohammad F (2008). "Aiming for the heart: targeted delivery of drugs to diseased cardiac tissue". Expert Opinion on Drug Delivery. 5 (4): 459–70.

[9] Chari, R. V. Targeted Delivery of Chemotherapeutics: Tumor-activated Prodrug Therapy. Adv Drug Deliv Rev 31, 89-104 (1998).

[10] van Bree, C., Castro Kreder, N., Loves, W. J., Franken, N. A., Peters, G. J., Haveman, J. Sensitivity to Ionizing Radiation and Chemotherapeutic Agents in Gemcitabine-resistant Human Tumor Cell Lines. Int J Radiat Oncol Biol Phys 54, 237-244 (2002).

[11] Krishna, R., Mayer, L. D. Multidrug Resistance (MDR) in Cancer. Mechanisms, Reversal Using Modulators of MDR and the Role of MDR Modulators in Influencing the Pharmacokinetics of Anticancer Drugs. Eur J Pharm Sci 11, 265-283 (2000).

[12] Bennis, S., Chapey, C., Couvreur, P., Robert, J. Enhanced Cytotoxicity of Doxorubicin Encapsulated in Polyisohexylcyanoacrylate Nanospheres Against Multidrug-resistant Tumour Cells in Culture. Eur J Cancer 30A, 89-93 (1994).

[13] Faneyte, I. F., Kristel, P. M., van de Vijver, M. J. Determining MDR1/P-glycoprotein Expression in Breast Cancer. Int J Cancer 93, 114-122 (2001).

[14] Molinari, A., Calcabrini, A., Meschini, S., Stringaro, A., Crateri, P., Toccacieli, L., Marra, M., Colone, M., Cianfriglia, M., Arancia, G. Subcellular Detection and Localization of the Drug Transporter Pglycoprotein in Cultured Tumor Cells. Curr Protein Pept Sci 3, 653-670 (2002).

[15] de Verdiere, A. C., Dubernet, C., Nemati, F., Soma, E., Appel, M., Ferte, J., Bernard, S., Puisieux, F., Couvreur, P. Reversion of Multidrug Resistance with Polyalkylcyanoacrylate Nanoparticles: Towards a Mechanism of Action. Br J Cancer 76, 198-205 (1997)

[16] Maeda, H., Seymour, L. W., Miyamoto, Y. Conjugates of Anticancer Agents and Polymers: Advantages of Macromolecular Therapeutics In Vivo. Bioconjug Chem 3, 351-362 (1992).

[17] Lasic, D. D. Doxorubicin in Sterically Stabilized Liposomes. Nature 380, 561-562 (1996).

[18] Kakizawa, Y., Kataoka, K. Block Copolymer Micelles for Delivery of Gene and Related Compounds. Adv Drug Deliv Rev 54, 203-222 (2002).

[19] Kataoka, K., Harada, A., Nagasaki, Y. Block Copolymer Micelles for Drug Delivery: Design, Characterization and Biological Significance. Adv Drug Deliv Rev 47, 113-131 (2001).

[20] Calcabrini, A., Meschini, S., Stringaro, A., Cianfriglia, M., Arancia, G., Molinari, A. Detection of P-glycoprotein in the Nuclear Envelope of Multidrug Resistant Cells. Histochem J 32, 599-606 (2000).

[21] Fu, L. W., Zhang, Y. M., Liang, Y. J., Yang, X. P., Pan, Q. C. The Multidrug Resistance of Tumour Cells was Reversed by Tetrandrine In Vitro and in Xenografts Derived from Human Breast Adenocarcinoma MCF-7/adr Cells. Eur J Cancer 38, 418-426 (2002).

[22] Arancia, G., Molinari, A., Calcabrini, A., Meschini, S., Cianfriglia, M. Intracellular P- glycoprotein in Multidrug Resistant Tumor Cells. Ital J Anat Embryol 106, 59-68 (2001).

[23] Minko, T., Paranjpe, P. V., Qiu, B., Lalloo, A., Won, R., Stein, S., Sinko, P. J. Enhancing the Anticancer Efficacy of Camptothecin Using Biotinylated Poly(ethylene glycol) Conjugates in Sensitive and Multidrug-resistant Human Ovarian Carcinoma Cells.Cancer Chemother Pharmacol 50, 143-150 (2002).

[24] Sahoo, S. K., Labhasetwar, V. Enhanced Antiproliferative Activity of Transferrin-conjugated Paclitaxel-loaded Nanoparticles is Mediated via Sustained Intracellular Drug Retention. Mol Pharm. in press (2005).

[25] Sagnella, S.; Drummond, C. Drug Delivery: A Nanomedicine Approach. AustralianBiochemist. [Online] 2012, 43, 5–8, 20. The Australian Society for Biochemistry and Molecular Biology.

[26] Vlerken, L. E. V.; Vyas, T. K.; Amiji, M. M. Poly(Ethylene Glycol)-Modified Nanocarriers for Tumor-Targeted and Intracellular Delivery. Pharm. Res. 2007, 24, 1405–1414.

[27] Jump up to:a b Gullotti, E.; Yeo, Y. Extracellularly Activated Nanocarriers: A New Paradigm of Tumor Targeted Drug Delivery. Mol. Pharm., [Online] 2009, 6, 1041-1051. ACS Publications.

[28] Matsumura Y, Maeda H (December 1986). "A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs". Cancer Research. 46 (12 Pt 1): 6387–92.