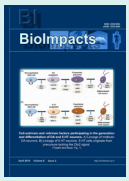
Barar J., Omidi Y., ***BioImpacts,*** 2015, 5(2), 65-69
doi: 10.15171/bi.2015.18
http://bi.tbzmed.ac.ir/

Personalized cell-mediated immunotherapy and vaccination: combating detrimental uprisings of malignancies

Jaleh Barar*, Yadollah Omidi*

Research Center for Pharmaceutical Nanotechnology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

Article Info



Article Type:
Editorial

Article History:
Received: 20 Apr. 2015
Accepted: 24 Apr. 2015
ePublished: 26 Apr. 2015

Keywords:
Cancer
Cell therapy
Immunization
Immunotherapy
Personalized medicine
Solid tumors
Tumor microenvironment
Vaccination

Summary

A large number of researchers worldwide have conducted various investigations to advance the cell-based immunotherapies and to examine their clinical benefits as an ultimate prevention and/or treatment modalities against life-threatening malignancies. This dominion needs integration of science and technology to change the face of treatment of diseases towards much more personalized medicines. It is now plausible to reprogram the human cells for the prevention and treatment of diseases through various mechanisms such as modulation of immune system, nonetheless we should understand the complexity of biological functions of the cells in a holistic way to be able to manipulate the central dogma of the life to prevent any inadvertent mistake. We should, if not must, comprehend the interrelations of the cellular components (e.g., transport machineries) in the developmental processes of diseases. Still, we do not have a complete image of life, perhaps as expressive barcodes, and many pieces are missing. While completing this puzzle to picture the whole image and examine new treatment modalities, we should take extra caution upon unknown/little-known biological phenomena because trifling modulation/alteration in the complex systems of the life may result in tremendous impacts. In short, it seems we need to consider malignancies as complex systems and treat them in a holistic manner by targeting its hallmarks. Taken all, the immune system reinforcement would be one of the main foundations in combating detrimental malignancy uprising.

Authors Biosketch

Professor Jaleh Barar obtained her PhD degree (2004) in Pharmaceutical Cell Biology from Cardiff University, UK. Since then, she has worked at the Faculty of Pharmacy, Tabriz University of Medical Sciences (Iran), and the Perelman School of Medicine at the University of Pennsylvania (USA), teaching and conducting researches on various aspects of molecular pharmaceutics. Her main research interest is cancer drug delivery and targeting through exploitation of advanced novel multifunctional nanosystems for simultaneous diagnosis and therapy in different malignancies.

Professor Yadollah Omidi obtained his PhD degree (2003) in Pharmaceutical Sciences (brain drug delivery and targeting) from Cardiff University (UK) and then completed a postdoctoral program (2004) in Pharmaceutical Nanobiotechnology (gene-based nanomedicines) at Cardiff University. He is the founder of the Research Center for Pharmaceutical Nanotechnology (RCPN), the School of Advanced Biomedical Sciences at Tabriz University of Medical Sciences (TUOMS), the international peer-review multidisciplinary journal "*BioImpacts*", and the national curriculum for PhD program in Pharmaceutical Nanotechnology. Prof. Omidi's researches in advanced targeted diagnosis and therapy of diseases have resulted in over 120 published papers in international journals, 12 book chapters, and a few patents. During 20 years of experiences in different institutes (Cardiff University, UK; TUOMS, Iran; and University of Pennsylvania, USA), his scientific life has been endowed with the integrative translational researches in a bench-to-bedside direction.

Immunization of cancer

After successful accomplishment of a number of studies as "proof-of-concept" upon the cell-based vaccinations, the first "proof-of-technology" and more realistically "proof-of-marketing" was emerged as sipuleucel-T (also known as APC8015/Provenge™) by Dendreon Corp. (Seattle, WA, USA). Sipuleucel-T was approved by the United State Food and Drug Administration (FDA) in 2010 for the treatment of prostate cancer, which showed evidence of efficacy in lessening mortality risk among men with metastatic castration-resistant prostate cancer (MCRPC).[1-3]As the first FDA approved autologous active cellular immunotherapy modality, Sipuleucel-T opened a new horizon for the cancer therapy and raised great hopes for the development of futuristic personalized immunotherapies and vaccines. For the proof-of-technology, Kantoff et al carried out a double-blind multicenter phase III trial, in which randomly assigned 512 patients were administered either sipuleucel-T (341 patients) or placebo (171 patients) intravenously every

***Corresponding authors:** Jaleh Barar, Email: jbarar@tbzmed.ac.ir; Yadollah Omidi, Email: yomidi@tbzmed.ac.ir

© 2015 The Author(s). This work is published by BioImpacts as an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by-nc/4.0/). Non-commercial uses of the work are permitted, provided the original work is properly cited.

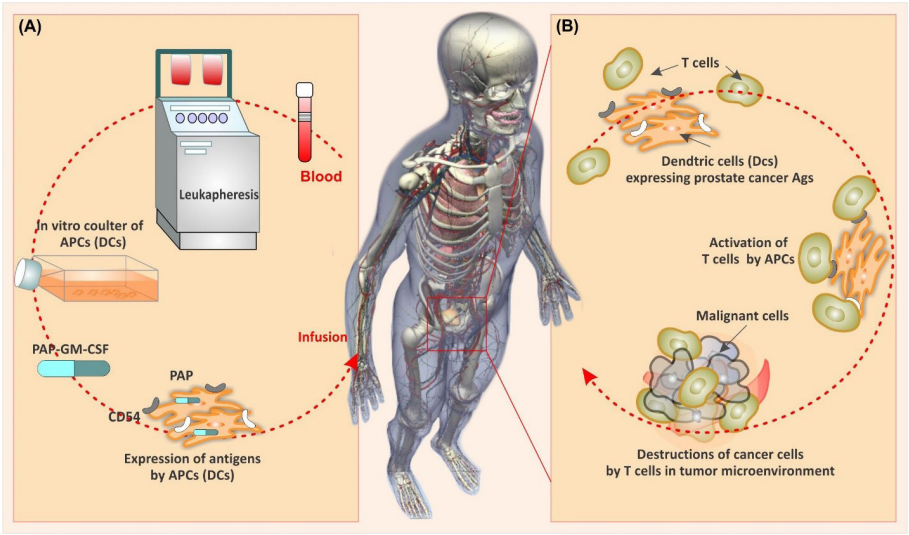


Fig. 1. Schematic representation for the cell-based sipuleucel-T immunotherapy of prostate cancer. A) Necessary steps applied for accomplishing the cell-based treatment modality. B) Sipuleucel-T (Provenge™) mechanism of action. Treatment commences with the isolation of dendritic cells (DCs) as antigen presenting cells (APCs) from the patient undergone for Provenge™ therapy. Then, after in vitro cultivation of the DCs in the presence of fusion protein PAP–GM-CSF composed of prostate acid phosphatase (PAP) and granulocyte–macrophage colony-stimulating factor (GM–CSF) as immune responses enhancer (panel A), the reprogramed DCs expressing CD54 and PAP are re-infused into the patient to activate T cells response against the prostate cancer cells (panel B). Image was adapted with permission form our previously published work.[5] Note: not drawn to scale.

2 weeks – three infusions in total. In the group treated with sipuleucel-T, in comparison with the group treated with placebo, a significant reduction (22%) in the risk of death was observed with 36-month survival probability of 31.7%.[2]

As the first personalized medicine, sipuleucel-T has successfully been used for the treatment of asymptomatic/minimally symptomatic metastatic hormone-refractory prostate cancer (HRPC).[3,4] Fig. 1 schematically epitomizes the cell-based immunotherapy process using sipuleucel-T modality.

As shown in Fig. 1, the administration of sipuleucel-T needs three key steps of (*a*) isolation of the patient's antigen-presenting cells (APCs) such as dendritic cells (DCs) using a leukapheresis system, (*b*) incubation of the isolated cells with the fusion protein PA2024, which consists of the antigen prostatic acid phosphatase (PAP) and an immune signaling factor granulocyte-macrophage colony stimulating factor (GM-CSF), to reprogram the patient's APCs to present the required antigens, and (*c*) infusion of the activated blood product.

It should be noted that during invasion and metastasis in the most, if not all, of malignancies, traveling single cancer cells escape the "anoikis" phenomenon that is the main mechanism of death program for the homeless single cells unanchored the extracellular matrix. In 2004, Douma et al showed that the functional expression of TrkB protein favors cancer cells to run away the anoikis, in which the brain-derived neurotrophic factor (BDNF) stimulated TrkB protein can in turn activate the AKT/PKB proteins whose functions result in survival and proliferation of separated traveling cancer cells.[6] Since then, several studies revealed that cancer cells recruit various bioelements to escape the anoikis.[7-14] Taken all, some pivotal questions still remain unanswered, for example we must know how can really homeless single cancerous cells survive the anoikis and immunosurveillance? And, how effective would be the applied vaccination/immunotherapy against malignancies if some cancerous cells alter its characteristics to evade the immune system functions? We believe that the transitional alteration of differentiated cancer cells to the undedicated cancer stem cells, which can act as progenitor for the second colonization and relapse, is possible mechanism for the survival of single cancer cell invaders even though the detailed mechanism(s) by which invading tumor cells survive the anoikis process are yet to be fully understood.

So far, the chemotherapy of cancer has associated with some important shortcomings such as inadvertent side effects in the healthy cells, leading many scientists including our group to search for more cancer-specific treatment modalities such as multimodal nanomedicines and seamless theranostics.[15-21] In addition, success of the currently used immunotherapy of cancer appears to be associated with some difficulties,[22-25] so are the gene therapy modalities, while the gene delivery viral vectors[26,27] and nonviral vectors[28-34] respectively induce intrinsic immunogenicity and genotoxicity.

In the case of cancer immunotherapy, two key strategies have currently been utilized for the tumor targeting, including (*a*) the antibody-directed targeting of toxic agents or cytolytic activity and (*b*) intensification of cellular immune responses against malignant cells. However, these approaches have resulted in limited successes, largely because of (*a*) the inadequate penetration and dissemination of antibodies (Abs) or Ab-conjugates in the tumor microenvironment (TME) as well as cancer cells

and (*b*) the trivial activation of tumor-specific cytotoxic lymphocytes.[35] In fact, in the solid tumors, the TME forms a permissive milieu with unique characteristics, inclusing (*a*) altered energetic pathways; for example glucose is hugely metabolized via glycolysis in favor of fueling of the lenient milieu of TME and remodeling of the extracellular matrix (ECM), (*b*) acidified extracellular fluid within the TME to reprogram the ECM and stromal cells in favor of the further invasion and metastasis, (*c*) transformed metabolism profile for some important biomolecules; for example, L-tryptophan is metabolized to produce kynurenine to favor the cancer cells to escape the anticancer immunosurveillance function of immune system and immunotherapies, (*d*) reprogramed stromal cells, (*e*) altered tumor interstitial fluid with high oncotic pressure, and (*f*) changed pattern of drug penetration into the core of solid tumor, in which passive diffusion no longer is the key player, and convection and migration phenomena of molecules/macromolecules impact dissemination of endogenous/exogenous compounds/particulates within TME.[36,37]

Within the TME, even the transportation of the macromolecular nanosystems (NSs) through different paths (e.g., diffusion, migration and/or convection) would entirely differ from that of the normal tissues/cells. The tumor interstitial fluid pressure (IFP) is markedly high and hence the penetration of macromolecular anticancer agents into the deep core of solid tumor, where encompasses the cancer stem cells, appears to be intriguingly low in solid tumors. Further, the high microvascular density in the primary tumor is often associated with increased incidence of lymph node metastases as well as poor clinical outcome,[38] and tumors with high IFP were reported to be dense in microvasculature in the periphery but possess large hypoxic fractions centrally. Hence, all these issues can limit the anticancer activity of immune system and immunotherapies.[39]

Up until now, a large number of clinical trials have been conducted for the cell-mediated vaccination of solid tumors, most of which were based on the use of tumor cells vaccines, modified lymphocytes and reprogramed APCs such as DCs to stimulate the immune responses through both CD4+ T helper cells and CD8+ cytotoxic T-lymphocytes (CTLs).[40-44] Of these studies, implementation of fused DCs and tumor cells hybrids (the so-called dentritoma) seems to be a promising strategy even though some important inadequacies may limit its clinical usefulness as reported for DCs-based vaccination in the late stage melanoma.[45] Combined immunotherapy and antivascular therapy has been proposed as an effective therapeutic modality in mice model bearing B16-F10 melanoma tumors to polarize the TME using a tumor cell-based vaccine (CAMEL peptide as a B16-F10 cell death-inducing agent). The combined therapy was found to induce profound inhibitory impacts as compared to monotherapies, resulting in lessened angiogenesis and increased tumor-infiltrating CD4+, CD8+ and NK cells with lowered suppressor T-lymphocytes (Tregs).[46] Table 1 represents some selected clinical trials on the cell-based vaccination of cancer.

Taken all, to tackle such hurdles, most of the strategies have been based on the enhancement of the immune system activity, for which the cell-based modalities against malignancies have been capitalized on the modulation of dendritic cells and/or lymphocytes.[41,43,47-49] In these approaches, the foundation of immunotherapy is based on the reprograming of cellular elements of immune system towards modulation of both the innate and adaptive immunity of the patient.

Despite accomplishment of a large number of promising translational researches and clinical trials on the cell-based vaccination, still we do not have an ultimate immunization

Table 1. Selected clinical trials for the cell-based vaccination of solid tumors

Vaccination modality	Trial description	Cancer	Phase, status	Clinical trial identifier
Autologous Ad HER2 dendritic cell vaccine	Ad/HER2/Neu dendritic cell cancer vaccine testing	Breast	I, recruiting	NCT01730118
Aldesleukin, filgrastim, anti-p53 T-cell receptor-transduced peripheral blood lymphocytes, autologous dendritic cell-adenovirus p53 vaccine	Gene-modified lymphocytes, high-dose aldesleukin, and vaccine therapy in treating patients with progressive or recurrent metastatic cancer	Various solid tumors	II, terminated with results	NCT00704938
DEC-205/NY-ESO-1 fusion protein CDX-1401	Vaccine therapy with or without sirolimus in treating patients with NY-ESO-1 expressing solid tumors	Various solid tumors	I, active, not recruiting	NCT01522820
CAP 1-6D and CMVpp65 peptide-pulsed, autologous dendritic cells	Vaccine therapy in treating patients with refractory stage IV cancer	Unspecified adult solid tumors	I, completed	NCT00057915
Dendritic cell vaccine loaded with autologous tumor	Autologous OC-DC vaccine in ovarian cancer	Ovarian cancer	0, recruiting	NCT01132014
Tumor Associated Peptide Antigens (TAPAz)-pulsed DC vaccine	Treatment of patients with progressive and/or refractory solid malignancies	Various solid tumors	I/II, just initiated	NCT02224599
Dendritic cell-gp100-MART-1 antigen vaccine	Vaccine therapy in treating patients with high-risk stage III or completely resected metastatic melanoma	Stage III/IV melanoma	II, completed	NCT00019890

strategy against solid tumors. We believe that the status of TME in different solid tumors and penetration of macromolecules and immune system cells into such microenvironments must be fully understood. Further, we must address some pivotal issues to make sure upon the clinical benefits of the cell-based vaccination strategy. We need to answer some key questions. How effective would be the cell-based vaccination strategy if the core of solid tumors hosts some undedicated cancer stem cells (CSCs)? If such assumption is true, then what would be the best strategy for targeting CSCs? What would be the behavior of immune system components within TME with acidified tumor interstitial fluid and high oncotic pressure? Ideally, the use of panel of cancer molecular markers (CMMs) involved in TME[50,51] can be beneficial for the development of the cell-based immunotherapies and vaccination which will literally benefit both the antibody-directed and cell-mediated immunotherapy, and hence improve the survival rate. Thus, key CMMs of TME should be recognized. To this end, we need to comprehend the whole panel of molecular event in the TME as complex systems and design the cell-based immunization/vaccination in a holistic manner for each cancer patient exclusively.

Acknowledgments

Authors are very grateful to Tabriz University of Medical Sciences for hosting the "Publish Free" and "Access Free" journal "*BioImpacts*", which is an international platform for publication of the bench-to-beside translational researches in the field of pharmaceutical and biomedical sciences.

Ethical issues

There is none to be declared.

Competing interests

There is none to be disclosed.

References

1. Higano CS, Small EJ, Schellhammer P, Yasothan U, Gubernick S, Kirkpatrick P, *et al.* Sipuleucel-T. *Nat Rev Drug Discov* **2010**; 9: 513-4. doi:10.1038/nrd3220
2. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, *et al.* Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* **2010**; 363: 411-22. doi:10.1056/NEJMoa1001294
3. Di Lorenzo G, Buonerba C, Kantoff PW. Immunotherapy for the treatment of prostate cancer. *Nat Rev Clin Oncol* **2011**; 8: 551-61. doi:10.1038/nrclinonc.2011.72
4. Huber ML, Haynes L, Parker C, Iversen P. Interdisciplinary critique of sipuleucel-T as immunotherapy in castration-resistant prostate cancer. *J Natl Cancer Inst* **2012**; 104: 273-9. doi:10.1093/jnci/djr514
5. Barar J, Omidi Y. Translational Approaches towards Cancer Gene Therapy: Hurdles and Hopes. *Bioimpacts* **2012**; 2: 127-43. doi:10.5681/bi.2012.025
6. Douma S, Van Laar T, Zevenhoven J, Meuwissen R, Van Garderen E, Peeper DS. Suppression of anoikis and induction of metastasis by the neurotrophic receptor TrkB. *Nature* **2004**; 430: 1034-9. doi:10.1038/nature02765
7. Liotta LA, Kohn E. Anoikis: cancer and the homeless cell. *Nature* **2004**; 430: 973-4. doi:10.1038/430973a
8. Wang SC, Makino K, Xia W, Kim JS, Im SA, Peng H, *et al.* DOC-2/hDab-2 inhibits ILK activity and induces anoikis in breast cancer cells through an Akt-independent pathway. *Oncogene* **2001**; 20: 6960-4. doi:10.1038/sj.onc.1204873
9. Normanno N, De Luca A, Bianco C, Maiello MR, Carriero MV, Rehman A, *et al.* Cripto-1 overexpression leads to enhanced invasiveness and resistance to anoikis in human MCF-7 breast cancer cells. *J Cell Physiol* **2004**; 198: 31-9. doi:10.1002/jcp.10375
10. Yang JM, O'Neill P, Jin W, Foty R, Medina DJ, Xu Z, *et al.* Extracellular matrix metalloproteinase inducer (CD147) confers resistance of breast cancer cells to Anoikis through inhibition of Bim. *J Biol Chem* **2006**; 281: 9719-27. doi:10.1074/jbc.M508421200
11. Cameron HL, Foster WG. Dieldrin promotes resistance to anoikis in breast cancer cells in vitro. *Reprod Toxicol* **2008**; 25: 256-62. doi:10.1016/j.reprotox.2007.11.013
12. Liu G, Meng X, Jin Y, Bai J, Zhao Y, Cui X, *et al.* Inhibitory role of focal adhesion kinase on anoikis in the lung cancer cell A549. *Cell Biol Int* **2008**; 32: 663-70. doi:10.1016/j.cellbi.2008.01.292
13. Shen W, Chen D, Fu H, Liu S, Sun K, Sun X. S100A4 protects gastric cancer cells from anoikis through regulation of alphav and alpha5 integrin. *Cancer Sci* **2011**; 102: 1014-8. doi:10.1111/j.1349-7006.2011.01915.x
14. Campos MS, Neiva KG, Meyers KA, Krishnamurthy S, Nor JE. Endothelial derived factors inhibit anoikis of head and neck cancer stem cells. *Oral Oncol* **2012**; 48: 26-32. doi:10.1016/j.oraloncology.2011.09.010
15. Matthaiou EI, Barar J, Sandaltzopoulos R, Li C, Coukos G, Omidi Y. Shikonin-loaded antibody-armed nanoparticles for targeted therapy of ovarian cancer. *Int J Nanomedicine* **2014**; 9: 1855-70. doi:10.2147/IJN.S51880
16. Mashinchian O, Johari-Ahar M, Ghaemi B, Rashidi M, Barar J, Omidi Y. Impacts of quantum dots in molecular detection and bioimaging of cancer. *Bioimpacts* **2014**; 4: 149-66. doi:10.15171/bi.2014.008
17. Heidari Majd M, Barar J, Asgari D, Valizadeh H, Rashidi MR, Kafil V, *et al.* Targeted fluoromagnetic nanoparticles for imaging of breast cancer mcf-7 cells. *Adv Pharm Bull* **2013**; 3: 189-95. doi:10.5681/apb.2013.031
18. Heidari Majd M, Asgari D, Barar J, Valizadeh H, Kafil V, Coukos G, *et al.* Specific targeting of cancer cells by multifunctional mitoxantrone-conjugated magnetic nanoparticles. *J Drug Target* **2013**; 21: 328-40. doi:10.3109/1061186X.2012.750325
19. Heidari Majd M, Asgari D, Barar J, Valizadeh H, Kafil V, Abadpour A, *et al.* Tamoxifen loaded folic acid armed PEGylated magnetic nanoparticles for targeted imaging and therapy of cancer. *Colloids Surf B Biointerfaces* **2013**; 106: 117-25. doi:10.1016/j.colsurfb.2013.01.051
20. Omidi Y. Smart multifunctional theranostics: simultaneous diagnosis and therapy of cancer. *Bioimpacts* **2011**; 1: 145-7. doi:10.5681/bi.2011.019
21. Mooguee M, Omidi Y, Davaran S. Synthesis and in vitro release of adriamycin from star-shaped poly(lactide-co-glycolide) nano- and microparticles. *J Pharm Sci* **2010**; 99: 3389-97. doi:10.1002/jps.22106
22. Tohidkia MR, Asadi F, Barar J, Omidi Y. Selection of potential therapeutic human single-chain Fv antibodies against cholecystokinin-B/gastrin receptor by phage display technology. *BioDrugs* **2013**; 27: 55-67. doi:10.1007/s40259-012-0007-0
23. Kafil V, Baradaran B, Omidi Y. What role can bispecific antibodies play in cancer targeting? A hypothesis. *Med Hypotheses* **2013**; 81: 44-6. doi:10.1016/j.mehy.2013.03.022
24. Rezaiemanesh A, Majidi J, Baradaran B, Movasaghpour A, Nakhlband A, Barar J, *et al.* Impacts of anti-EGFR monoclonal antibody in prostate cancer PC3 cells. *Hum Antibodies* **2010**; 19: 63-70. doi:10.3233/HAB-2010-0229
25. Majidi J, Barar J, Baradaran B, Abdolalizadeh J, Omidi Y. Target therapy of cancer: implementation of monoclonal antibodies and nanobodies. *Hum Antibodies* **2009**; 18: 81-100. doi:10.3233/HAB-2009-0204

26. Wilson JM. Lessons learned from the gene therapy trial for ornithine transcarbamylase deficiency. *Mol Genet Metab* **2009**; 96: 151-7. doi:10.1016/j.ymgme.2008.12.016
27. Thomas CE, Ehrhardt A, Kay MA. Progress and problems with the use of viral vectors for gene therapy. *Nat Rev Genet* **2003**; 4: 346-58. doi:10.1038/nrg1066
28. Barar J, Omidi Y. Intrinsic bio-signature of gene delivery nanocarriers may impair gene therapy goals. *Bioimpacts* **2013**; 3: 105-9. doi:10.5681/bi.2013.028
29. Kafil V, Omidi Y. Cytotoxic impacts of linear and branched polyethylenimine nanostructures in a431 cells. *Bioimpacts* **2011**; 1: 23-30. doi:10.5681/bi.2011.004
30. Omidi Y, Barar J, Heidari HR, Ahmadian S, Yazdi HA, Akhtar S. Microarray analysis of the toxicogenomics and the genotoxic potential of a cationic lipid-based gene delivery nanosystem in human alveolar epithelial a549 cells. *Toxicol Mech Methods* **2008**; 18: 369-78. doi:10.1080/15376510801891286
31. Hollins AJ, Omidi Y, Benter IF, Akhtar S. Toxicogenomics of drug delivery systems: Exploiting delivery system-induced changes in target gene expression to enhance siRNA activity. *J Drug Target* **2007**; 15: 83-8. doi:10.1080/10611860601151860
32. Omidi Y, Hollins AJ, Drayton RM, Akhtar S. Polypropylenimine dendrimer-induced gene expression changes: the effect of complexation with DNA, dendrimer generation and cell type. *J Drug Target* **2005**; 13: 431-43. doi:10.1080/10611860500418881
33. Omidi Y, Barar J, Akhtar S. Toxicogenomics of cationic lipid-based vectors for gene therapy: impact of microarray technology. *Curr Drug Deliv* **2005**; 2: 429-41.
34. Omidi Y, Hollins AJ, Benboubetra M, Drayton R, Benter IF, Akhtar S. Toxicogenomics of non-viral vectors for gene therapy: a microarray study of lipofectin- and oligofectamine-induced gene expression changes in human epithelial cells. *J Drug Target* **2003**; 11: 311-23. doi:10.1080/10611860310001636908
35. Chen SY, Yang AG, Chen JD, Kute T, King CR, Collier J, *et al.* Potent antitumour activity of a new class of tumour-specific killer cells. *Nature* **1997**; 385: 78-80. doi:10.1038/385078a0
36. Barar J, Omidi Y. Dysregulated pH in Tumor Microenvironment Checkmates Cancer Therapy. *Bioimpacts* **2013**; 3: 149-62. doi:10.5681/bi.2013.036
37. Barar J. Targeting tumor microenvironment: the key role of immune system. *Bioimpacts* **2012**; 2: 1-3. doi:10.5681/bi.2012.001
38. Rofstad EK, Galappathi K, Mathiesen BS. Tumor interstitial fluid pressure-a link between tumor hypoxia, microvascular density, and lymph node metastasis. *Neoplasia* **2014**; 16: 586-94. doi:10.1016/j.neo.2014.07.003
39. Omidi Y, Barar J. Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. *Bioimpacts* **2014**; 4: 55-67. doi:10.5681/bi.2014.021
40. de Rosa F, Fanini F, Guidoboni M, Vannini I, Amadori D, Ridolfi R, *et al.* MicroRNAs and dendritic cell-based vaccination in melanoma patients. *Melanoma Res* **2014**; 24: 181-9. doi:10.1097/CMR.0000000000000058
41. Wang J, Liao L, Tan J. Dendritic cell-based vaccination for renal cell carcinoma: challenges in clinical trials. *Immunotherapy* **2012**; 4: 1031-42. doi:10.2217/imt.12.107
42. Oshita C, Takikawa M, Kume A, Miyata H, Ashizawa T, Iizuka A, *et al.* Dendritic cell-based vaccination in metastatic melanoma patients: phase II clinical trial. *Oncol Rep* **2012**; 28: 1131-8. doi:10.3892/or.2012.1956
43. Saito H, Frleta D, Dubsky P, Palucka AK. Dendritic cell-based vaccination against cancer. *Hematol Oncol Clin North Am* **2006**; 20: 689-710. doi:10.1016/j.hoc.2006.02.011
44. Stift A, Friedl J, Dubsky P, Bachleitner-Hofmann T, Schueller G, Zontsich T, *et al.* Dendritic cell-based vaccination in solid cancer. *J Clin Oncol* **2003**; 21: 135-42.
45. Schneble EJ, Yu X, Wagner TE, Peoples GE. Novel dendritic cell-based vaccination in late stage melanoma. *Hum Vaccin Immunother* **2014**; 10: 3132-8. doi:10.4161/hv.29110
46. Jarosz-Biej M, Smolarczyk R, Cichon T, Kulach N, Czapla J, Matuszczak S, *et al.* Combined Tumor Cell-Based Vaccination and Interleukin-12 Gene Therapy Polarizes the Tumor Microenvironment in Mice. *Arch Immunol Ther Exp (Warsz)* **2015**. doi:10.1007/s00005-015-0337-y
47. Fujii S, Takayama T, Asakura M, Aki K, Fujimoto K, Shimizu K. Dendritic cell-based cancer immunotherapies. *Arch Immunol Ther Exp (Warsz)* **2009**; 57: 189-98. doi:10.1007/s00005-009-0025-x
48. Nestle FO, Farkas A, Conrad C. Dendritic-cell-based therapeutic vaccination against cancer. *Curr Opin Immunol* **2005**; 17: 163-9. doi:10.1016/j.coi.2005.02.003
49. Ji YH, Weiss L, Zeira M, Abdul-Hai A, Reich S, Schuger L, *et al.* Allogeneic cell-mediated immunotherapy of leukemia with immune donor lymphocytes to upregulate antitumor effects and downregulate antihost responses. *Bone Marrow Transplant* **2003**; 32: 495-504. doi:10.1038/sj.bmt.1704150
50. Baronzio G, Parmar G, Baronzio M, Kiselevsky M. Tumor interstitial fluid: proteomic determination as a possible source of biomarkers. *Cancer Genomics Proteomics* **2014**; 11: 225-37.
51. Gromov P, Gromova I, Olsen CJ, Timmermans-Wielenga V, Talman ML, Serizawa RR, *et al.* Tumor interstitial fluid - a treasure trove of cancer biomarkers. *Biochim Biophys Acta* **2013**; 1834: 2259-70. doi:10.1016/j.bbapap.2013.01.013