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Topic: Cancer Stem Cells: Impact on Treatment

Therapeutic strategies for targeting cancer stem cells

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Dr. Yu Jeong Kim is a PhD candidate in the Department of Pharmacology and Pharmaceutical Science at University of Southern California (USC) mentored by Dr. Pin Wang. Her research focuses on liposomal nanoparticle-based drug delivery for combination therapy such as co-delivering two inhibitors to target two distinct populations within tumor bulk. Current studies involve the combination of immunotherapy and existing chemotherapeutic drug by utilizing Chimeric Antigen Receptor (CAR)-engineered T cells and Natural Killer (NK) cells and pharmaceutical drugs loaded crosslinked multilayer liposome vesicles for targeted cancer therapy.

ABSTRACT

The therapeutic limitations of conventional chemotherapeutic drugs present a challenge for cancer therapy; these shortcomings are largely attributed to the ability of cancer cells to repopulate and metastasize after initial therapies. Compelling evidence suggests that cancer stem cells (CSCs) have a crucial impact in current shortcomings of cancer therapy because they are largely responsible for tumor initiation, relapse, metastasis, and chemo-resistance. Thus, a better understanding of the properties and mechanisms underlying CSC resistance to treatments is necessary to improve patient outcomes and survival rates. In this review, the authors characterize and compare different CSC-specific biomarkers that are present in various types of tumors. We further discuss multiple targeting approaches currently in preclinical or clinical testing that show great potential for targeting CSCs. This review discusses numerous strategies to eliminate CSCs by targeting surface biomarkers, regulating CSC-associated oncogenes and signaling pathways, inhibiting drug-efflux pumps involved in drug resistance, modulating the tumor microenvironment and immune system, and applying drug combination therapy using nanomedicine.

Key words: Cancer stem cells; targeted cancer therapy; drug resistance

INTRODUCTION

Cancer stem cells (CSCs) are a small subset of cancer cells with the ability to self-renew and initiate tumor growth. They were first discovered in acute myeloid leukemia (AML) in the late 1990s.[1] Since then, CSCs have been discovered in many solid tumors.[2-6] Within the last two decades, CSCs have become a subject of intense research as a potential target for cancer therapeutics.

The discovery of CSCs led to a major shift in cancer modeling. Previously, cancers were thought to be made up of equipotent malignant cells which either renewed or differentiated stochastically, giving rise to a heterogeneous tumor. In contrast, the CSC model suggests that a hierarchy exists among tumor cells, with CSCs at the top, producing the bulk of the tumor cells while maintaining their own renewal.[5] A third model, clonal evolution, states that heterogeneity comes from genetic or epigenetic changes that arise during cancer progression. The CSC and clonal evolution models are not mutually exclusive, as CSCs can also evolve over time, generating different clonal subpopulations within the tumor.[6]

CSCs share a number of properties with normal stem cells (SCs). Both typically make up a small percentage of the total number of cells in a tissue, they are largely quiescent, and, most notably, they are multipotent and

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As discussed above, nanocarriers enhanced the delivery and cytotoxic activity of CSC-inhibitors. Several studies introduced active targeting strategies of nanoparticle surfaces to increase their specificity and cellular uptake by CSCs. Lastly, researchers have been focusing on nanoparticle-mediated drug combinatorial therapy. One important advantage of nanocarriers is their capability to incorporate multiple therapeutic agents in one carrier system, allowing co-delivery of cytotoxic drugs and CSC inhibitors to simultaneously target both bulk tumor and CSCs. Patient cures will rely on the ablation of the entire tumor. Ultimately, nanoparticle mediated combination therapy may prove to be the most successful in eradicating whole tumors.

The CSC field is relatively new, and CSC-targeting therapeutics is in their early stages. While many advances have been made in CSC research, many of these studies have been performed *in vitro* only, and none are past the early clinical stages. Important factors such as effective dosages and side effects must be elucidated before employing cancer treatment plans that target both differentiated tumor cells and CSCs. There is need to improve the existing methods to precisely isolate, identify and target CSCs. As mentioned, increasing amount of nanomedicine have been evaluated about their application potentials in CSC therapy, but only a small amount of them can be approved to translate to clinical treatment. With the fact that every cancer acts differently in different patients, the development of personalized combinational therapies may serve as a key to successful treatments. Furthermore, it is important to realize that the combination of nanomedicine and immunotherapy may present a novel direction which shows great potential in personalized cancer therapy.

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Conflicts of interests

There are no conflicts of interest.

REFERENCES

1. Bonnet D, Dick JE. J. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med* 1997;3:730-7.
2. Al-Hajj M, Wicha M, Benito-Hernandez A, Morrison S, Clarke M. Prospective identification of tumorigenic breast cancer cells. *PNAS* 2003;100:3983-8.
3. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, Dirks PB. Identification of a cancer stem cell in human brain tumors. *Cancer Res* 2003;63:5821-8.
4. Kim CF, Jackson EL, Woolfenden AE, Lawrence S, Babar I, Vogel S, Crowley D, Bronson RT, Jacks T. Identification of bronchioalveolar stem cells in normal lung and lung cancer. *Cell* 2005;121:823-35.
5. Beck B, Blanpain C. Unravelling cancer stem cell potential. *Nat Rev Cancer* 2013;13:727-38.
6. Chen K, Huang YH, Chen JL. Understanding and targeting cancer stem cells: therapeutic implications and challenges. *Acta Pharmacol Sin* 2013;34:732-40.
7. Wang J, Sullenger BA, Rich JN. Notch signaling in cancer stem cells. *Adv Exp Med Biol* 2012;727:174-85.
8. Hambardzumyan D1, Becher OJ, Rosenblum MK, Pandolfi PP, Manova-Todorova K, Holland EC. PI3K pathway regulates survival of cancer stem cells residing in the perivascular niche following radiation in medulloblastoma *in vivo*. *Genes Dev* 2008;22:436-48.
9. Campbell V, Copland M. Hedgehog signaling in cancer stem cells: a focus on hematological cancers. *Stem Cells Cloning* 2015;8:27-38.
10. Simões BM, O'Brien CS, Eyre R, Silva A, Yu L, Sarmiento-Castro A, Alférez DG, Spence K, Santiago-Gómez A, Chemi F, Acar A, Gandhi A, Howell A, Brennan K, Rydén L, Catalano S, Andó S, Gee J, Ucar A, Sims AH, Marangoni E, Farnie G, Landberg G, Howell SJ, Clarke RB. Anti-estrogen resistance in human breast tumors is driven by JAG1-NOTCH4-dependent cancer stem cell activity. *Cell Rep* 2015;12:1968-77.
11. Bleau AM, Hambardzumyan D, Ozawa T, Fomchenko EI, Huse JT, Brennan CW, Holland EC. PTEN/PI3K/Akt pathway regulates the side population phenotype and ABCG2 activity in glioma tumor stem-like cells. *Cell Stem Cell* 2009;4:226-35.
12. Bautch VL. Stem cells and the vasculature. *Nat Med* 2011;17:1437-43.
13. Price JE, Polyzos A, Zhang RD, Daniels LM. Tumorigenicity and metastasis of human breast carcinoma cell lines in nude mice. *Cancer Res* 1990;50:717-21.
14. Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, Viale A, Olshen AB, Gerald WL, Massagué J. Genes that mediate breast cancer metastasis to lung. *Nature* 2005;436:518-24.
15. Allahverdiyev AM, Bagirova M, Oztel ON, Yaman S, Abamor ES, Koc RC, Ates SC, Elcicek S, Baydar SY. Aldehyde Dehydrogenase: Cancer and Stem Cells. In: Canuto RA, editor. Dehydrogenases. InTech; Rijeka, Croatia: 2012. pp. 3-28.
16. Duan JJ, Qiu W, Xu SL, Wang B, Ye XZ, Ping YF, Zhang X, Bian XW, Yu SC. Strategies for isolating and enriching cancer stem cells: well begun is half done. *Stem Cells Dev* 2013;22:2221-39.
17. Sheridan C, Kishimoto H, Fuchs RK, Mehrotra S, Bhat-Nakshatri P, Turner CH, Goulet R Jr, Badve S, Nakshatri H. CD44+/CD24- breast cancer cells exhibit enhanced invasive properties: an early step necessary for metastasis. *Breast Cancer Res* 2006;8:R59.
18. Klonisch T, Wiechec E, Hombach-Klonisch S, Ande SR, Wesselborg S, Schulze-Osthoff K, Los M. Cancer stem cell markers in common cancers - therapeutic implications. *Trends Mol Med* 2008;10:450-60.
19. Ali HR, Dawson SJ, Blows FM, Provenzano E, Pharoah PD, Caldas C. Cancer stem cell markers in breast cancer: pathological, clinical and prognostic significance. *Breast Cancer Res* 2011;6:R118.
20. Tirino V, Desiderio V, Paino F, De Rosa A, Papaccio F, La Noce M, Laino L, De Francesco F, Papaccio G. Cancer stem cells in solid tumors: an overview and new approaches for their isolation and characterization. *FASEB J* 2013;1:13-24.
21. Greve B, Kelsch R, Spaniol K, Eich HT, Götte M. Flow cytometry in cancer stem cell analysis and separation. *Cytometry A* 2012;4:284-93.
22. Komuro H, Saihara R, Shinya M, Takita J, Kaneko S, Kaneko M, Hayashi Y. Identification of side population cells (stem-like cell population) in pediatric solid tumor cell lines. *J Pediatr Surg* 2007;42:2040-5.
23. Miranda-Lorenzo I, Dorado J, Lonardo E, Alcala S, Serrano AG, Clausell-Tormos J, Cioffi M, Megias D, Zagorac S, Balic A,

Hidalgo M, Erkan M, Kleeff J, Scarpa A, Sainz B Jr, Heeschen C. Intracellular autofluorescence: a biomarker for epithelial cancer stem cells. *Nat Methods* 2014;11:1161-9.
24. Cao L, Zhou Y, Zhai B, Liao J, Xu W, Zhang R, Li J, Zhang Y, Chen L, Qian H, Wu M, Yin Z. Sphere-forming cell subpopulations with cancer stem cell properties in human hepatoma cell lines. *BMC Gastroenterol* 2011;11:71.
25. Wang K, Wu X, Wang J, Huang J. Cancer stem cell theory: therapeutic implications for nanomedicine. *Int J Nanomedicine* 2013;8:899-908.
26. Smalley M, Piggott L, Clarkson R. Breast cancer stem cells: obstacles to therapy. *Cancer Lett* 2013;338:57-62.
27. Suman S, Das TP, Damodaran C. Silencing NOTCH signaling causes growth arrest in both breast cancer stem cells and breast cancer cells. *Br J Cancer* 2013;109:2587-96.
28. Zang S, Chen F, Dai J, Guo D, Tse W, Qu X, Ma D, Ji C. RNAi-mediated knockdown of Notch-1 leads to cell growth inhibition and enhanced chemosensitivity in human breast cancer. *Oncol Rep* 2010;23893-9.
29. Gupta S, Takebe N, Lorusso P. Targeting the Hedgehog pathway in cancer. *Ther Adv Med Oncol* 2010;2:237-50.
30. Zhao C, Chen A, Jamieson CH, Fereshteh M, Abrahamsson A, Blum J, Kwon HY, Kim J, Chute JP, Rizzieri D, Munchhof M, VanArsdale T, Beachy PA, Reya T. Hedgehog signalling is essential for maintenance of cancer stem cells in myeloid leukaemia. *Nature* 2009;458:776-9.
31. Berman DM, Karhadkar SS, Hallahan AR, Pritchard JI, Eberhart CG, Watkins DN, Chen JK, Cooper MK, Taipale J, Olson JM, Beachy PA. Medulloblastoma growth inhibition by hedgehog pathway blockade. *Science* 2002;297:1559-61.
32. Thayer SP, di Magliano MP, Heiser PW, Nielsen CM, Roberts DJ, Lauwers GY, Qi YP, Gysin S, Fernández-del Castillo C, Yajnik V, Antoniu B, McMahon M, Warshaw AL, Hebrok M. Hedgehog is an early and late mediator of pancreatic cancer tumorigenesis. *Nature* 2003;425:851-6.
33. Zeilstra J, Joosten SP, Dokter M, Verwiel E, Spaargaren M, Pals ST. Deletion of the WNT target and cancer stem cell marker CD44 in Apc(Min/+) mice attenuates intestinal tumorigenesis. *Cancer Res* 2008;68:3655-61.
34. Hallett RM, Kondratyev MK, Giacomelli AO, Nixon AM, Girgis-Gabardo A, Ilieva D, Hassell JA. Small molecule antagonists of the Wnt/β-catenin signaling pathway target breast tumor-initiating cells in a Her2/Neu mouse model of breast cancer. *PLoS One* 2012;7:e33976.
35. Gu W, Yeo E, McMillan N, Yu C. Silencing oncogene expression in cervical cancer stem-like cells inhibits their cell growth and self-renewal ability. *Cancer Gene Ther* 2011;18:897-905.
36. Puca F, Colamaio M, Federico A, Gemei M, Tosti N, Bastos AU, Del Vecchio L, Pece S, Battista S, Fusco A. HMGA1 silencing restores normal stem cell characteristics in colon cancer stem cells by increasing p53 levels. *Oncotarget* 2014;5:3234-45.
37. Wang T, Gantier MP, Xiang D, Bean AG, Bruce M, Zhou SF, Khasraw M, Ward A, Wang L, Wei MQ, AlShamaileh H, Chen L, She X, Lin J, Kong L, Shigdar S, Duan W. EpCAM aptamer-mediated survivin silencing sensitized cancer stem cells to doxorubicin in a breast cancer model. *Theranostics* 2015;5:1456-72.
38. Deonarain MP, Kousparou CA, Epenetos AA. Antibodies targeting cancer stem cells: a new paradigm in immunotherapy? *MAbs* 2009;1:12-25.
39. Zinzi L, Contino M, Cantore M, Capparelli E, Leopoldo M, Colabufo NA. ABC transporters in CSCs membranes as a novel target for treating tumor relapse. *Front Pharmacol* 2014;5:163.
40. Morrison R, Schleicher SM, Sun Y, Niermann KJ, Kim S, Spratt DE, Chung CH, Lu B. Targeting the mechanisms of resistance to chemotherapy and radiotherapy with the cancer stem cell hypothesis. *J Oncol* 2011;2011:941876.
41. Vaz AP, Ponnusamy MP, Batra SK. Cancer stem cells and therapeutic targets: an emerging field for cancer treatment. *Drug Deliv Transl Res* 2013;3:113-20.
42. Ding PR, Tiwari AK, Ohnuma S, Lee JW, An X, Dai CL, Lu QS, Singh S, Yang DH, Talele TT, Ambudkar SV, Chen ZS. The phosphodiesterase-5 inhibitor vardenafil is a potent inhibitor of ABCB1/P-glycoprotein transporter. *PLoS One* 2011;6:e19329.
43. Calcagno AM, Salcido CD, Gillet JP, Wu CP, Fostel JM, Mumau MD, Gottesman MM, Varticovski L, Ambudkar SV. Prolonged drug selection of breast cancer cells and enrichment of cancer stem cell characteristics. *J Natl Cancer Inst* 2010;102:1637-52.
44. Dönmez Y, Gündüz U. Reversal of multidrug resistance by small interfering RNA (siRNA) in doxorubicin-resistant MCF-7 breast cancer cells. *Biomed Pharmacother* 2011;65:85-9.
45. Li X, Li P, Zhang Y, Zhou Y, Chen X, Huang Y, Liu Y. Novel Mixed Polymeric Micelles for Enhancing Delivery of Anticancer Drug and Overcoming Multidrug Resistance in Tumor Cell Lines Simultaneously. *Pharm Res* 2010;27:1498-511.
46. Šubr V, Koziolová E, Sivák L, Říhová B, Kovář M, Ulbrich K. Polymer inhibitors of ABC transporter overcoming multidrug resistance: Synthesis, characterization and *in vitro* evaluation. *J Control Release* 2015;213:e107-8.
47. Falasca M, Linton KJ. Investigaional ABC transporter inhibitors. *Expert Opin Investig Drugs* 2012;21:657-66.
48. Schatton T, Frank MH. Antitumor immunity and cancer stem cells. *Ann N Y Acad Sci* 2009;1176:154-69.
49. Lee PP, Yee C, Savage PA, Fong L, Brockstedt D, Weber JS, Johnson D, Swetter S, Thompson J, Greenberg PD, Roederer M, Davis MM. Characterization of circulating T cells specific for tumor-associated antigens in melanoma patients. *Nat Med* 1999;5:677-85.
50. Khong HT, Wang QJ, Rosenberg SA. Identification of multiple antigens recognized by tumor-infiltrating lymphocytes from a single patient: tumor escape by antigen loss and loss of MHC expression. *J Immunother* 2004;27:184-90.
51. Ames E, Canter RJ, Grossenbacher SK, Mac S, Chen M, Smith RC, Hagino T, Perez-Cunningham J, Sckisel GD, Urayama S, Monjazeb AM, Fragoso RC, Sayers TJ, Murphy WJ. NK Cells Preferentially Target Tumor Cells with a Cancer Stem Cell Phenotype. *J Immunol* 2015;195:4010-9.
52. Ahmadzadeh M, Rosenberg SA. IL-2 administration increases CD4+ CD25(hi) Foxp3+ regulatory T cells in cancer patients. *Blood* 2006;107:2409-14.
53. Rosenberg SA, Yang JC, Topalian SL, Schwartzentruber DJ, Weber JS, Parkinson DR, Seipp CA, Einhorn JH, White DE. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. *JAMA* 1994;271:907-13.
54. Rosenberg SA, Mulé JJ, Spiess PJ, Reichert CM, Schwarz SL. Regression of established pulmonary metastases and subcutaneous tumor mediated by the systemic administration of high-dose recombinant interleukin 2. *J Exp Med* 1985;161:1169-88.
55. Itoh K, Platsoucas CD, Balch CM. Autologous tumor-specific cytotoxic T lymphocytes in the infiltrate of human metastatic melanomas. Activation by interleukin 2 and autologous tumor cells, and involvement of the T cell receptor. *J Exp Med* 1988;168:1419-41.
56. Powell DJ Jr, de Vries CR, Allen T, Ahmadzadeh M, Rosenberg SA. Inability to mediate prolonged reduction of regulatory T Cells after transfer of autologous CD25-depleted PBMC and interleukin-2 after lymphodepleting chemotherapy. *J Immunother* 2007;30:438-47.
57. Canter RJ, Grossenbacher SK, Ames E, Murphy WJ. Immune targeting of cancer stem cells in gastrointestinal oncology. *J*

Gastrointest Oncol 2016;7 Suppl 1:S1-10.
58. Deng Z, Wu Y, Ma W, Zhang S, Zhang YQ. Adoptive T-cell therapy of prostate cancer targeting the cancer stem cell antigen EpCAM. *BMC Immunol* 2015;16:1.
59. Zhu X, Prasad S, Gaedicke S, Hettich M, Firat E, Niedermann G. Patient-derived glioblastoma stem cells are killed by CD133-specific CAR T cells but induce the T cell aging marker CD57. *Oncotarget* 2015;6:171-84.
60. Schmidt P, Kopecky C, Hombach A, Zigrino P, Mauch C, Abken H. Eradication of melanomas by targeted elimination of a minor subset of tumor cells. *Proc Natl Acad Sci U S A* 2011;108:2474-9.
61. Beard RE, Zheng Z, Lagisetty KH, Burns WR, Tran E, Hewitt SM, Abate-Daga D, Rosati SF, Fine HA, Ferrone S, Rosenberg SA, Morgan RA. Multiple chimeric antigen receptors successfully target chondroitin sulfate proteoglycan 4 in several different cancer histologies and cancer stem cells. *J Immunother Cancer* 2014;2:25.
62. Morgan RA, Johnson LA, Davis JL, Zheng Z, Woolard KD, Reap EA, Feldman SA, Chinnasamy N, Kuan CT, Song H, Zhang W, Fine HA, Rosenberg SA. Recognition of glioma stem cells by genetically modified T cells targeting EGFRvIII and development of adoptive cell therapy for glioma. *Hum Gene Ther* 2012;23:1043-53.
63. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, Roche PC, Lu J, Zhu G, Tamada K, Lennon VA, Celis E, Chen L. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. *Nat Med* 2002;8:793-800.
64. Riley JL, Mao M, Kobayashi S, Biery M, Burchard J, Cavet G, Gregson BP, June CH, Linsley PS. Modulation of TCR-induced transcriptional profiles by ligation of CD28, ICOS, and CTLA-4 receptors. *Proc Natl Acad Sci U S A* 2002;99:11790-5.
65. Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. *Annu Rev Immunol* 2007;25:267-96.
66. Wing K, Onishi Y, Prieto-Martin P, Yamaguchi T, Miyara M, Fehervari Z, Nomura T, Sakaguchi S. CTLA-4 control over Foxp3+ regulatory T cell function. *Science* 2008;322:271-5.
67. Tarhini AA, Iqbal F. CTLA-4 blockade: therapeutic potential in cancer treatments. *Onco Targets Ther* 2010;3:15-25.
68. Hu Y, Fu L. Targeting cancer stem cells: a new therapy to cure cancer patients. *Am J Cancer Res* 2012;2:340-56.
69. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, Akerley W, van den Eertwegh AJ, Lutzky J, Lorigan P, Vaubel JM, Linette GP, Hogg D, Ottensmeier CH, Lebbé C, Peschel C, Quirt I, Clark JI, Wolchok JD, Weber JS, Tian J, Yellin MJ, Nichol GM, Hoos A, Urba WJ. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-23.
70. Fong L, Small EJ. Anti-cytotoxic T-lymphocyte antigen-4 antibody: the first in an emerging class of immunomodulatory antibodies for cancer treatment. *J Clin Oncol* 2008;26:5275-83.
71. Langer LF, Clay TM, Morse MA. Update on anti-CTLA-4 antibodies in clinical trials. *Expert Opin Biol Ther* 2007;7:1245-56.
72. Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, Rietz C, Flies DB, Lau JS, Zhu G, Tamada K, Chen L. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res* 2005;65:1089-96.
73. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol* 2004;173:945-54.
74. FDA approves new, targeted treatment for bladder cancer: Tecentriq is the first PD-L1 inhibitor approved by the FDA. Food and Drug Administration, FDA News Release 2016.
75. Kawasaki BT, Farrar WL. Cancer Stem Cells, CD200 and Immunoevasion. *Trends Immunol* 2008;29:464-8.
76. Kawasaki BT, Mistree T, Hurt EM, Kalathur M, Farrar WL. Co-expression of the toleragenic glycoprotein, CD200, with markers for cancer stem cells. *Biochem Biophys Res Commun* 2007;364:778-82.
77. Jung YS, Vermeer PD, Vermeer DW, Lee SJ, Goh AR, Ahn HJ, Lee JH. CD200: association with cancer stem cell features and response to chemoradiation in head and neck squamous cell carcinoma. *Head Neck* 2015;37:327-35.
78. McWhirter JR, Kretz-Rommel A, Saven A, Maruyama T, Potter KN, Mockridge CI, Ravey EP, Qin F, Bowdish KS. Antibodies selected from combinatorial libraries block a tumor antigen that plays a key role in immunomodulation. *Proc Natl Acad Sci U S A* 2006;103:1041-6.
79. Gorczynski RM, Chen Z, Hu J, Kai Y, Lei J. Evidence of a role for CD200 in regulation of immune rejection of leukaemic tumour cells in C57BL/6 mice. *Clin Exp Immunol* 2001;126:220-9.
80. Siva A, Xin H, Qin F, Oltean D, Bowdish KS, Kretz-Rommel A. Immune modulation by melanoma and ovarian tumor cells through expression of the immunosuppressive molecule CD200. *Cancer Immunol Immunother* 2008;57:987-96.
81. Korkaya H, Liu S, Wicha MS. Regulation of cancer stem cells by cytokine networks: attacking cancer's inflammatory roots. *Clin Cancer Res* 2011;17:6125-9.
82. Persano L, Rampazzo E, Basso G, Viola G. Glioblastoma cancer stem cells: role of the microenvironment and therapeutic targeting. *Biochem Pharmacol* 2013;85:612-22.
83. Charles N, Holland EC. The perivascular niche microenvironment in brain tumor progression. *Cell Cycle* 2010;9:3012-21.
84. Scheller J, Rose-John S. Interleukin-6 and its receptor: from bench to bedside. *Med Microbiol Immunol* 2006;195:173-83.
85. Trikha M, Corringham R, Klein B, Rossi JF. Targeted anti-interleukin-6 monoclonal antibody therapy for cancer: a review of the rationale and clinical evidence. *Clin Cancer Res* 2003;9:4653-65.
86. Guo Y, Xu F, Lu T, Duan Z, Zhang Z. Interleukin-6 signaling pathway in targeted therapy for cancer. *Cancer Treat Rev* 2012;38:904-10.
87. Ginestier C, Liu S, Diebel ME, Korkaya H, Luo M, Brown M, Wicinski J, Cabaud O, Charafe-Jauffret E, Birnbaum D, Guan JL, Dontu G, Wicha MS. CXCR1 blockade selectively targets human breast cancer stem cells *in vitro* and in xenografts. *J Clin Invest* 2010;120:485-97.
88. Hartman ZC, Poage GM, den Hollander P, Tsimelzon A, Hill J, Panupinthu N, Zhang Y, Mazumdar A, Hilsenbeck SG, Mills GB, Brown PH. Growth of triple-negative breast cancer cells relies upon coordinate autocrine expression of the proinflammatory cytokines IL-6 and IL-8. *Cancer Res* 2013;73:3470-80.
89. Burroughs SK, Kaluz S, Wang D, Wang K, Van Meir EG, Wang B. Hypoxia inducible factor pathway inhibitors as anticancer therapeutics. *Future Med Chem* 2013;5:553-72.
90. Batchelor TT, Duda DG, di Tomaso E, Ancukiewicz M, Plotkin SR, Gerstner E, Eichler AF, Drappatz J, Hochberg FH, Benner T, Louis DN, Cohen KS, Chea H, Exarhopoulos A, Loeffler JS, Moses MA, Ivy P, Sorensen AG, Wen PY, Jain RK. Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol* 2010;28:2817-23.
91. Pan E, Yu D, Yue B, Potthast L, Chowdhary S, Smith P, Chamberlain M. A prospective phase II single-institution trial of sunitinib for recurrent malignant glioma. *J Neurooncol* 2012;110:111-8.
92. Brossa A, Grange C, Mancuso L, Annaratone L, Satolli MA, Mazzone M, Camussi G, Bussolati B. Sunitinib but not VEGF blockade inhibits cancer stem cell endothelial differentiation. *Oncotarget* 2015;6:11295-309.

93. Garcia A, Singh H. Bevacizumab and ovarian cancer. *Ther Adv Med Oncol* 2013;5:133-41.
94. Krishnamurthy S, Ke X, Yang YY. Delivery of therapeutics using nanocarriers for targeting cancer cells and cancer stem cells. *Nanomedicine (Lond)* 2015;10:143-60.
95. Gupta PB, Onder TT, Jiang G, Tao K, Kuperwasser C, Weinberg RA, Lander ES. Identification of selective inhibitors of cancer stem cells by high-throughput screening. *Cell* 2009;138:645-59.
96. Malhi S, Gu X. Nanocarrier-mediated drugs targeting cancer stem cells: an emerging delivery approach. *Expert Opin Drug Deliv* 2015;12:1177-201.
97. Shen S, Xia JX, Wang J. Nanomedicine-mediated cancer stem cell therapy. *Biomaterials* 2016;74:1-18.
98. Zhao Y, Alakhova DY, Kabanov AV. Can nanomedicines kill cancer stem cells? *Adv Drug Deliv Rev* 2013;65:1763-83.
99. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC. Cancer nanotechnology: the impact of passive and active targeting in the era of modern cancer biology. *Adv Drug Deliv Rev* 2014;66:2-25.
100. Liu Y, Rohrs J, Wang P. Advances and challenges in the use of nanoparticles to optimize PK/PD interactions of combined anti-cancer therapies. *Curr Drug Metab* 2014;15:818-28.
101. Swaminathan SK, Roger E, Toti U, Niu L, Ohlfest JR, Panyam J. CD133-targeted paclitaxel delivery inhibits local tumor recurrence in a mouse model of breast cancer. *J Control Release* 2013;171:280-7.
102. Vinogradov S, Wei X. Cancer stem cells and drug resistance: the potential of nanomedicine. *Nanomedicine (Lond)* 2012;7:597-615.
103. Xiao H, Li W, Qi R, Yan L, Wang R, Liu S, Zheng Y, Xie Z, Huang Y, Jing X. Co-delivery of daunomycin and oxaliplatin by biodegradable polymers for safer and more efficacious combination therapy. *J Control Release* 2012;163:304-14.
104. Kim YJ, Liu Y, Li S, Rohrs J, Zhang R, Zhang X, Wang P. Co-Eradication of Breast Cancer Cells and Cancer Stem Cells by Cross-Linked Multilamellar Liposomes Enhances Tumor Treatment. *Mol Pharm* 2015;12:2811-22.
105. Oak PS, Kopp F, Thakur C, Ellwart JW, Rapp UR, Ullrich A, Wagner E, Knyazev P, Roidl A. Combinatorial treatment of mammospheres with trastuzumab and salinomycin efficiently targets HER2-positive cancer cells and cancer stem cells. *Int J Cancer* 2012;131:2808-19.