Stem Cell Therapy for Cancer Research Literatures

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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Key words: stem cell; cancer; therapy; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies. **Stem-cell therapy** is the use of stem cells to treat or prevent a disease or condition.

The following introduces recent reports as references in the related studies.

Aglietta, M., et al. (2009). "Reduced-intensity allogeneic hematopoietic stem cell transplantation in metastatic colorectal cancer as a novel adoptive cell therapy approach. The European group for blood and marrow transplantation experience." Biol Blood Marrow Transplant **15**(3): 326-335.

Reduced-intensity conditioning (RIC) regimens for allogeneic hematopoietic stem cell transplantation (HCT) allowed the existence of an allogeneic cell-mediated antitumor effect in metastatic colorectal cancer (mCRC) to be explored. We report on 39 patients with progressing mCRC treated with different RIC regimens in a multicenter clinical trial of the European Bone Marrow Transplantation Group. Disease status at transplant was progressive disease (PD) in 31 patients (80%), stable disease (SD) in 6 (15%), and partial response (PR) in 2 (5%). All patients engrafted (median donor T cell chimerism of 90% at day +60). Transplant-related morbidities were limited. Grades II-IV acute graft-versus-host disease (aGVHD) occurred in 14 patients (35%) and chronic GVHD (cGVHD) in 9 patients (23%). Transplant-related mortality occurred in 4 patients (10%). The best tumor responses were: 1 complete response (CR) (2%), 7 PR (18 %), and 10 SD (26%), giving an overall disease control in 18 of 39 patients (46%). Allogeneic HCT after RIC is feasible; the collected results compared favorably in terms of tumor response with those observed using conventional approaches beyond second-line therapies. The study of an allogeneic cell based therapy in less advanced patients is warranted.

Alessandrino, F., et al. (2017). "Imaging of hepatic toxicity of systemic therapy in a tertiary cancer centre: chemotherapy, haematopoietic stem cell transplantation, molecular targeted therapies, and immune checkpoint inhibitors." Clin Radiol **72**(7): 521-533.

The purpose of this review is to familiarise radiologists with the spectrum of hepatic toxicity seen in the oncology setting, in view of the different systemic therapies used in cancer patients. Drug-induced liver injury can manifest in various forms, and anti-neoplastic agents are associated with different types of hepatotoxicity. Although chemotherapy-induced liver injury can present as hepatitis, steatosis, sinusoidal obstruction syndrome, and chronic parenchymal damages, molecular targeted therapy-associated liver toxicity ranges from mild liver function test elevation to fulminant life-threatening acute liver failure. The recent arrival of immune checkpoint inhibitors in oncology has introduced a

new range of immune-related adverse events, with differing mechanisms of liver toxicity and varied imaging presentation of liver injury. High-dose chemotherapy regimens for haematopoietic stem cell transplantation are associated with sinusoidal obstruction syndrome. Management of hepatic toxicity depends on the clinical scenario, the drug in use, and the severity of the findings. In this article, we will (1) present the most common types of oncological drugs associated with hepatic toxicity and associated liver injuries; (2) illustrate imaging findings of hepatic toxicities and the possible differential diagnosis; and (3) provide a guide for management of these conditions.

Alperovich, M., et al. (2014). "Adipose stem cell therapy in cancer reconstruction: a critical review." Ann Plast Surg **73 Suppl 1**: S104-107.

Found in most mesenchymally derived organs, mesenchymal stem cells are undifferentiated cells capable of developing into many cell types. Adipose stem cells are a type of mesenchymal stem cell easily extracted from lipoaspirate, often readily available, and are conformable to the tissue defect. Their ability for self-renewal, unlimited proliferation and proangiogenic, and immunomodulatory properties have made them attractive adjuncts in plastic surgery. Since the discovery of pluripotent cells in adipose tissue, plastic surgeons have applied the technology toward improving wound healing, soft tissue augmentation, and tissue engineering. More recently, some surgeons have used adipose stem cells in cancer reconstruction. By mixing lipoaspirate with concentrated fractions of adipose stem cells through a technique termed cell-assisted lipotransfer, plastic surgeons have claimed improved aesthetic results. Promising early results have been tempered by in vitro and animal studies demonstrating increased tumor proliferation and metastasis rates with the use of adipose and other mesenchymal stem cells. This review provides a succinct yet comprehensive overview of the current literature evaluating the oncologic risks associated with adipose stem cell use in cancer.

Arya, M., et al. (2004). "Allogeneic hematopoietic stem-cell transplantation: the next generation of therapy for metastatic renal cell cancer." Nat Clin Pract Oncol **1**(1): 32-38.

The management of metastatic renal cell carcinoma (mRCC) remains a therapeutic challenge; less than 10% of patients survive for longer than 5 years. The resistance of renal cancer to chemotherapy may be explained by high levels of the multidrug resistance gene, MDR1. Immune-based treatments for renal cancer have been explored because of their unusual susceptibility to immunological assault. However, response rates to cytokines such as interleukin-2 and interferon-alpha have ranged from only 10% to 20%, prompting other immunotherapy approaches, such as allogeneic stem-cell transplantation, to be investigated. Several clinical trials have provided evidence of partial or complete disease regression in refractory mRCC following nonmyeloablative stem-cell transplantation. This effect is because of a donor antimalignancy effect mediated by immunocompetent donor T cells, called graft-versus-tumor effect. Unfortunately, less than 30% of patients who could have this procedure will have a human-leukocyte-antigen-compatible sibling, and attention is focusing on alternative donors such as matched unrelated donors and partially mismatched related donors. Despite the improved safety of nonmyeloablative conditioning regimens, transplant-related toxic effects (particularly graft-versus-host disease) remain obstacles to the safe and effective use of this treatment. Regardless of these limitations, innovative approaches have attempted to harness the potential of the graft-versus-tumor effect in mRCC and other solid tumors.

Bago, J. R., et al. (2016). "Fibrin matrices enhance the transplant and efficacy of cytotoxic stem cell therapy for post-surgical cancer." Biomaterials **84**: 42-53.

Tumor-homing cytotoxic stem cell (SC) therapy is a promising new approach for treating the incurable brain cancer glioblastoma (GBM). However, problems of retaining cytotoxic SCs within the post-surgical GBM resection cavity are likely to significantly limit the clinical utility of this strategy. Here, we describe a new fibrin-based transplant approach capable of increasing cytotoxic SC retention and persistence within the resection cavity, yet remaining permissive to tumoritropic migration. This fibrin-based transplant can effectively treat both solid and post-surgical human GBM in mice. Using our murine model of image-guided model of GBM resection, we discovered that suspending human mesenchymal stem cells (hMSCS) in a fibrin matrix increased initial retention in the surgical resection cavity 2-fold and prolonged persistence in the cavity 3-fold compared to conventional delivery strategies. Time-lapse motion analysis revealed that cytotoxic hMSCs in the fibrin matrix remain tumoritropic, rapidly migrating from the fibrin matrix to co-localize with cultured human GBM cells. We encapsulated hMSCs releasing the cytotoxic agent TRAIL (hMSC-sTR) in fibrin, and found hMSC-sTR/fibrin therapy reduced the viability of multiple 3-D human GBM spheroids and regressed established human GBM xenografts 3-fold in 11 days. Mimicking clinical therapy of surgically resected

GBM, intra-cavity seeding of therapeutic hMSC-sTR encapsulated in fibrin reduced post-surgical GBM volumes 6-fold, increased time to recurrence 4-fold, and prolonged median survival from 15 to 36 days compared to control-treated animals. Fibrin-based SC therapy could represent a clinically compatible, viable treatment to suppress recurrence of post-surgical GBM and other lethal cancer types.

Bago, J. R., et al. (2016). "Neural stem cell therapy for cancer." Methods **99**: 37-43.

Cancers of the brain remain one of the greatest medical challenges. Traditional surgery and chemo-radiation therapy are unable to eradicate diffuse cancer cells and tumor recurrence is nearly inevitable. In contrast to traditional regenerative medicine applications, engineered neural stem cells (NSCs) are emerging as a promising new therapeutic strategy for cancer therapy. The tumor-homing properties allow NSCs to access both primary and invasive tumor foci, creating a novel delivery platform. NSCs engineered with a wide array of cytotoxic agents have been found to significantly reduce tumor volumes and markedly extend survival in preclinical models. With the recent launch of new clinical trials, the potential to successfully manage cancer in human patients with cytotoxic NSC therapy is moving closer to becoming a reality.

Bao, Q., et al. (2012). "Mesenchymal stem cell-based tumor-targeted gene therapy in gastrointestinal cancer." Stem Cells Dev **21**(13): 2355-2363.

Mesenchymal stem (or stromal) cells (MSCs) are nonhematopoietic progenitor cells that can be obtained from bone marrow aspirates or adipose tissue, expanded and genetically modified in vitro, and then used for cancer therapeutic strategies in vivo. Here, we review available data regarding the application of MSC-based tumor-targeted therapy in gastrointestinal cancer, provide an overview of the general history of MSC-based gene therapy in cancer research, and discuss potential problems associated with the utility of MSC-based therapy such as biosafety, immunoprivilege, transfection methods, and distribution in the host.

Bashey, A., et al. (2001). "Use of capecitabine as first-line therapy in patients with metastatic breast cancer relapsing after high-dose chemotherapy and autologous stem cell support." Clin Oncol (R Coll Radiol) **13**(6): 434-437.

High-dose chemotherapy with autologous stem cell support (HDC-ASCS) can produce high complete remission rates in patients with metastatic breast cancer (MBC). However, the majority of those so treated will relapse within 3 years. The ability of such patients to tolerate further myelosuppressive chemotherapy may be limited and the best therapy is undefined. In this retrospective study we assessed the role of capecitabine as initial therapy after relapse. Ten patients (median age = 47 years; oestrogen receptor-positive, n = 4; visceral disease, n = 6; prior anthracycline, n = 8, prior taxanes, n = 10), whose disease progressed at a median of 246 days (range 69-480) after HDC-ASCS and who were treated with capecitabine (2500 mg/m2 per day for 2 weeks of a 3-week cycle) as initial therapy for relapse, were assessed retrospectively for response and toxicity. They received a median of eight cycles (range 4-24) of capecitabine. The toxicities encountered while receiving capecitabine were: hand-foot syndrome (grade 1, n = 3; grade 2, n = 4; grade 3, n = 1); diarrhoea (grade 1, n = 1; grade 2, n = 3); nausea (n = 2) and fatigue (n = 5). Haematological toxicity was seen in only one patient. No patient required hospitalization for toxicity. Three achieved a complete remission, four a partial remission and three disease stabilization. After a median follow-up of 183 days from commencing capecitabine (range 97-540), all patients were alive and five were in remission. Five progressed after remissions that lasted between 63 and 252 days. Oral capecitabine is an active and well-tolerated agent when used alone as first-line therapy in patients who have relapsed after HDC-ASCS for MBC.

Bayat, S., et al. (2018). "HDACis (class I), cancer stem cell, and phytochemicals: Cancer therapy and prevention implications." Biomed Pharmacother **97**: 1445-1453.

Epigenetics is independent of the sequence events that physically affect the condensing of chromatin and genes expression. The unique epigenetic memories of various cells trigger exclusive gene expression profiling. According to different studies, the aberrant epigenetic signatures and impaired gene expression profiles are master occurrences in cancer cells in which oncogene and tumor suppressor genes are affected. Owing to the facts that epigenetic modifications are performed earlier than expression and are reversible, the epigenetic reprogramming of cancer cells could be applied potentially for their prevention, control, and therapy. The disruption of the acetylation signature, as a master epigenetic change in cancers, is related to the expression and the activity of HDACs. In this context, class I HDACs play a significant role in the regulation of cell proliferation and cancer. More recently, cancer stem cell (CSC) has been introduced as a minority population of tumor that is responsible for invasiveness, drug resistance, and relapse of cancers. It is now believed that controlling CSC via epigenetic reprogramming such as targeting HDACs could be

helpful in regulating the acetylation pattern of chromatin. Recently, a number of reports have introduced some phytochemicals as HDAC inhibitors. The use of phytochemicals with the HDAC inhibition property could be potentially efficient in overcoming the mentioned problems of CSCs. This review presents a perspective concerning HDAC-targeted phytochemicals to control CSC in tumors. Hopefully, this new route would have more advantages in therapeutic applications and prevention against cancer.

Bergh, J. (1995). "High-dose therapy with autologous bone marrow stem cell support in primary and metastatic human breast cancer. A review." Acta Oncol **34**(5): 669-674.

A dose-response relationship has been demonstrated for metastatic human breast cancer. This increased response using moderately increased doses is generally not translated into an improved survival. The use of high-dose therapy to selected patients with metastases/recurrence responding to conventional doses of polychemotherapy may lead to an improved survival tail. Conventional doses of polychemotherapy in the adjuvant setting will reduce the relative mortality by around 25% 10 years after primary diagnosis. The use of high-dose therapy supported by autologous bone marrow stem cells may be markedly more effective in the adjuvant setting, especially to high-risk patients, compared with standard polychemotherapy. Several randomized studies are being planned or have already started in order to answer different aspects of this issue.

Berry, D. A., et al. (2011). "High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials." J Clin Oncol **29**(24): 3214-3223.

PURPOSE: Adjuvant high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation (AHST) for high-risk primary breast cancer has not been shown to prolong survival. Individual trials have had limited power to show overall benefit or benefits within subsets. METHODS: We assembled individual patient data from 15 randomized trials that compared HDC versus control therapy without stem-cell support. Prospectively defined primary end points were relapse-free survival (RFS) and overall survival (OS). We compared the effect of HDC versus control by using log-rank tests and proportional hazards regression, and we adjusted for clinically relevant covariates. Subset analyses were by age, number of positive lymph nodes, tumor size, histology, hormone receptor (HmR) status, and human epidermal growth factor receptor 2 (HER2) status. RESULTS: Of 6,210 total patients (n = 3,118, HDC; n = 3,092 control), the median age was 46 years; 69% were premenopausal, 29% were postmenopausal, and 2% were unknown menopausal status; 49.5% were HmR positive; 33.5% were HmR negative, and 17% were unknown HmR status. The median follow-up was 6 years. After analysis was adjusted for covariates, HDC was found to prolong relapse-free survival (RFS; hazard ratio [HR], 0.87; 95% CI, 0.81 to 0.93; P <.001) but not overall survival (OS; HR, 0.94; 95% CI, 0.87 to 1.02; P =.13). For OS, no covariates had statistically significant interactions with treatment effect, and no subsets evinced a significant effect of HDC. Younger patients had a significantly better RFS on HDC than did older patients. CONCLUSION: Adjuvant HDC with AHST prolonged RFS in high-risk primary breast cancer compared with control, but this did not translate into a significant OS benefit. Whether HDC benefits patients in the context of targeted therapies is unknown.

Bhargav, H., et al. (2012). "Enhancement of cancer stem cell susceptibility to conventional treatments through complementary yoga therapy: possible cellular and molecular mechanisms." J Stem Cells **7**(4): 261-267.

Cancer stem cells (CSCs) are stem-like tumor populations that are reported to contribute towards tumor growth, maintenance and recurrence after therapy. Hypoxia increases CSC fraction and promotes acquisition of a stem-cell-like state. Cancer stem cells are critically dependant on the hypoxia-inducible factor-1 (HIF-1) for survival, self-renewal, tumor growth and maintenance of their undifferentiated phenotype. Recent researches show that stage of differentiation of the tumor cells is predictive of their susceptibility to natural killer cell (NK) cell mediated cytotoxicity and cancer stem cells are significant targets of NK cell cytotoxicity. Studies also show that reversion of tumor cells to a less-differentiated phenotype can be achieved by blocking NFkappaB. Yoga therapy (yogic lifestyle modifications encompassing physical postures, breathing practices, relaxation techniques and meditations) is known to modulate neural, endocrine and immune functions at the cellular level through influencing cell cycle control, aging, oxidative stress, apoptosis and several pathways of stress signaling molecules. Yoga therapy has also been shown to enhance natural killer cell activity and modulate stress and DNA damage in breast cancer patients receiving radiotherapy. Recent study found that brief daily yogic meditation may reverse the pattern of increased NFkappaB-related transcription of pro-inflammatory cytokines in leukocytes. Thus, yoga therapy has the potential to reduce cancer stem cell survival, self -renewal and tumor growth by modifying the tumor micro-environment through various mechanisms such as; 1) reducing HIF-1 activity by

enhanced oxygenation, 2) promoting NK cell activity directly (or indirectly through down regulating NFkappaB expression), thereby enhancing NK cell mediated CSC lysis, and 3) by minimizing the aberrant expressions or activities of various hormones, cytokines, chemokines and tumor signaling pathways. Yoga therapy may have a synergistic effect with conventional modalities of treatment in preventing cancer progression and recurrences.

Blagosklonny, M. V. (2007). "Cancer stem cell and cancer stemloids: from biology to therapy." Cancer Biol Ther **6**(11): 1684-1690.

It has become a cliche that cancer therapy fails because it does not target rare cancer stem cells (CSCs). Here we are discuss that this is not how therapy fails and not any cancer cell with stem-like properties is CSC. Paradoxically, CSCs must be resting to explain their resistance to therapy yet must be cycling to explain their persistence in cell culture. To solve contradictions, this article introduces the term cancer stemloids (or stem cell-like cells) to describe proliferating self-renewing cells. The stem cell hierarchy (stem--proliferating--terminal cells) exists exactly to separate self-renewal (immortality) from proliferation. Cancer stemloids break the stem cell hierarchy and eventually may replace other cells. While CSC is shielded from any selective pressure and therefore unable to drive tumor progression, cancer stemloids undergo clonal selection, accumulate mutations, thus determining tumor progression and therapeutic failures. Unlike CSC, cancer stemloids are a crucial target for cancer therapy, exactly because they proliferate. Furthermore, two normally mutually-exclusive properties (proliferation and stemness) provide a means to design therapy to kill cancer stemloids selectively without killing normal stem and non-stem cells. In contrast, true CSCs are not only a difficult, but also an insufficient and perhaps even an unnecessary therapeutic target, especially in advanced malignancies.

Bou-Khalil, J., et al. (2003). "Sequential high-dose alkylating therapy and stem cell support for high-risk stage III breast cancer." Breast J **9**(6): 472-477.

Patients who receive neoadjuvant chemotherapy for locally advanced breast cancer and have four or more ipsilateral axillary lymph nodes involved at surgery are at high risk for recurrence, with a median time to relapse of 18 months. We offered such patients high-dose chemotherapy with stem cell rescue. Patients received cyclophosphamide or paclitaxel and granulocyte colony-stimulating factor (G-CSF) to mobilize stem cells. Melphalan 140 mg/m2 was then given with stem cell rescue. Twenty-four to 35 days later, thiotepa 900 mg/m2 was given with stem cell rescue. Patients with hormone receptor-positive tumors received tamoxifen. We treated 14 patients in this fashion from 1995 to 1998. The mean age was 46.7 years. The majority of cancers were stage IIIB (79%). Thirteen women underwent mastectomy after anthracycline-containing chemotherapy and 50% had more than seven positive lymph nodes. Hospitalization was principally for neutropenic fever. Other morbidities were pneumonitis, cardiomyopathy, and grade 3/4 white blood cell (WBC) toxicity. No patient died of a treatment-related complication. Seven of 14 relapsed at 10, 12, <15, 15, 17, 21, and 36 months, with median follow-up of 26.5 months. Time to relapse in this small series is only modestly improved over historical experience with standard-dose adjuvant chemotherapy. Alternative strategies for treating locally advanced breast cancer should be pursued.

Brasseur, N., et al. (2000). "Eradication of multiple myeloma and breast cancer cells by TH9402-mediated photodynamic therapy: implication for clinical ex vivo purging of autologous stem cell transplants." Photochem Photobiol **72**(6): 780-787.

High-dose chemotherapy combined with autologous transplantation using bone marrow or peripheral blood-derived stem cells (PBSC) is now widely used in the treatment of hematologic malignancies as well as some solid tumors like breast cancer (BC). However, some controversial results were recently obtained in the latter case. The presence of malignant cells in the autograft has been associated with the recurrence of the disease, and purging procedures are needed to eliminate this risk. The aim of this study was to evaluate the potential of the photosensitizer 4,5-dibromorhodamine methyl ester (TH9402), a dibrominated rhodamine derivative, to eradicate multiple myeloma (MM) and BC cell lines, while sparing more than 50% of normal pluripotential blood stem cells from healthy volunteers. The human BC MCF-7 and T-47D and MM RPMI 8226 and NCI-H929 cell lines were used to optimize the photodynamic purging process. Cell concentration and the cell suspension thickness as well as the dye and light doses were varied in order to eventually treat 1-2 L of apheresis. The light source consisted of two fluorescent scanning tubes emitting green light centered about 515 nm. The cellular uptake of TH9402 was measured during the incubation and washout periods and after photodynamic treatment (PDT) using spectrofluorometric analysis. The limiting dilution assay showed that an eradication rate of more than 5 logs is obtained when using a 40 min incubation with 5-10 microM dye followed by a 90 min washout period and a light dose of 5-10 J/cm2 (2.8 mW/cm2) in all cell lines. Agitating the 2 cm thick cell suspension containing 20 x 10(6) cells/mL during PDT was

essential for maximal photoinactivation. Experiments on mobilized PBSC obtained from healthy volunteers showed that even more drastic purging conditions than those found optimal for maximal eradication of the malignant cell lines were compatible with a good recovery of hematopoietic progenitors cells. The absence of significant toxicity towards normal hematopoietic stem cells, combined with the 5 logs eradication of cancer cell lines induced by this procedure suggests that TH9402 offers an excellent potential as an ex vivo photodynamic purging agent for autologous transplantation in MM and BC treatment.

Buchholz, T. A., et al. (2000). "Importance of radiation therapy for breast cancer patients treated with high-dose chemotherapy and stem cell transplant." Int J Radiat Oncol Biol Phys **46**(2): 337-343.

PURPOSE: To determine local-regional failure rates in breast cancer patients treated with surgery and high-dose chemotherapy with stem cell transplant and to relate local-regional failure to the use and timing of radiation treatment. METHODS AND MATERIALS: We retrospectively reviewed the records of 165 breast cancer patients treated on institutional protocols with surgery and high-dose chemotherapy with stem cell transplant. All patients had either Stage III disease, 10 or more positive axillary lymph nodes, or 4 or more positive axillary lymph nodes following neoadjuvant chemotherapy. Twelve patients had inflammatory breast cancer. Thirteen patients treated with breast preservation and 5 patients who died from toxicity within 30 days of transplant were excluded from the analyses of local-regional recurrences. In the remaining 147 patients, 108 were treated with adjuvant radiation and 39 were not. The disease stage distribution for these two groups was comparable. The median follow-up for surviving patients was 35 months. RESULTS: The 3- and 5-year actuarial disease-free survival (DFS) for the entire group was 60% and 51%, respectively. The 5-year rates of freedom from isolated local-regional recurrence were 95% in the patients treated with adjuvant radiation and 86% in the patients who did not receive radiation ($p = 0.014$, log rank comparison). The 5-year rates of any local-regional recurrence as a first event (isolated recurrences plus those with simultaneous local-regional and distant recurrences) were 92% versus 82%, respectively for patients whose treatment did and did not include radiation ($p = 0.038$). We could not demonstrate a correlation of the timing of radiation with the risk of local-regional recurrence. CONCLUSIONS: These data indicate that high-dose chemotherapy does not negate the importance of radiation in optimizing local-regional control in patients with high-risk breast cancer. Given the results of recent randomized trials studying postmastectomy radiation, which show that improving local-regional control improves overall survival (OS), we believe that all breast cancer patients with high-risk primary breast cancer who are treated with high-dose chemotherapy with stem cell transplant should receive radiation as a component of their treatment.

Cacciari, N., et al. (2000). "The addition of topotecan to carboplatin and paclitaxel as first-line therapy for advanced ovarian cancer; is it possible only with peripheral blood stem cell support?" Eur J Gynaecol Oncol **21**(1): 84-85.

A phase I study was performed in order to evaluate the tolerability of the combination of fixed doses of carboplatin and paclitaxel and escalated doses of topotecan as first line chemotherapy for advanced epithelial ovarian cancer. Three stage III and one stage IV patients entered the study. The dose limiting toxicity (neutropenia and thrombocytopenia) was reached at the first dose level: paclitaxel 175 mg/m2 on day 1, carboplatin AUC 5 on day I and topotecan 0.5 mg/m2 daily from day 1 to day 3. We conclude that it is not possible to add topotecan to standard regimens of carboplatin and paclitaxel without bone marrow support.

Carnero, A., et al. (2016). "The cancer stem-cell signaling network and resistance to therapy." Cancer Treat Rev **49**: 25-36.

The study of cancer stem cells (CSCs) has shown that tumors are driven by a subpopulation of self-renewing CSCs that retain the capacity to engender the various differentiated cell populations that form tumors. The characterization of CSCs has indicated that CSCs are remarkably resistant to conventional radio- and chemo-therapy. Clinically, the remaining populations of CSC are responsible for metastasis and recurrence in patients with cancer, which can lead to the disease becoming chronic and incurable. Therefore, the elimination of CSCs is an important goal of cancer treatments. Furthermore, CSCs are subject to strong regulation by the surrounding microenvironment, which also impacts tumor responses. In this review, we discuss the mechanisms by which pathways that are defective in CSCs influence ultimately therapeutic and clinical outcomes.

Chae, Y. C. and J. H. Kim (2018). "Cancer stem cell metabolism: target for cancer therapy." BMB Rep **51**(7): 319-326.

Increasing evidence suggests that cancer stem cell (CSC) theory represents an important mechanism underlying the observed failure of existing therapeutic modalities to fully eradicate cancers. In addition to their more established role in maintaining minimal

residual disease after treatment and forming the new bulk of the tumor, CSCs might also critically contribute to tumor recurrence and metastasis. For this reason, specific elimination of CSCs may thus represent one of the most important treatment strategies. Emerging evidence has shown that CSCs have a different metabolic phenotype to that of differentiated bulk tumor cells, and these specific metabolic activities directly participate in the process of CSC transformation or support the biological processes that enable tumor progression. Exploring the role of CSC metabolism and the mechanism of the metabolic plasticity of CSCs has become a major focus in current cancer research. The targeting of CSC metabolism may provide new effective therapies to reduce the risk of recurrence and metastasis. In this review, we summarize the most significant discoveries regarding the metabolism of CSCs and highlight recent approaches in targeting CSC metabolism. [BMB Reports 2018; 51(7): 319-326].

Cheema, T. A., et al. (2013). "Multifaceted oncolytic virus therapy for glioblastoma in an immunocompetent cancer stem cell model." Proc Natl Acad Sci U S A **110**(29): 12006-12011.

Glioblastoma (World Health Organization grade IV) is an aggressive adult brain tumor that is inevitably fatal despite surgery, radiation, and chemotherapy. Treatment failures are attributed to combinations of cellular heterogeneity, including a subpopulation of often-resistant cancer stem cells, aberrant vasculature, and noteworthy immune suppression. Current preclinical models and treatment strategies do not incorporate or address all these features satisfactorily. Herein, we describe a murine glioblastoma stem cell (GSC) model that recapitulates tumor heterogeneity, invasiveness, vascularity, and immunosuppressive microenvironment in syngeneic immunocompetent mice and should prove useful for a range of therapeutic studies. Using this model, we tested a genetically engineered oncolytic herpes simplex virus that is armed with an immunomodulatory cytokine, interleukin 12 (G47-mIL12). G47Delta-mIL12 infects and replicates similarly to its unarmed oncolytic herpes simplex virus counterpart in mouse 005 GSCs in vitro, whereas in vivo, it significantly enhances survival in syngeneic mice bearing intracerebral 005 tumors. Mechanistically, G47-mIL12 targets not only GSCs but also increases IFN-gamma release, inhibits angiogenesis, and reduces the number of regulatory T cells in the tumor. The increased efficacy is dependent upon T cells, but not natural killer cells. Taken together, our findings demonstrate that G47Delta-mIL12 provides a multifaceted approach to targeting GSCs, tumor microenvironment, and the immune system, with resultant therapeutic benefit in a stringent glioblastoma model.

Chen, S. and E. H. Huang (2014). "The colon cancer stem cell microenvironment holds keys to future cancer therapy." J Gastrointest Surg **18**(5): 1040-1048.

BACKGROUND: Colorectal cancer remains the most common gastrointestinal cancer. While screening combined with effective surgical treatment has reduced its mortality, we still do not have effective means to prevent recurrence nor to treat metastatic disease. What we know about cancer biology has gone through revolutionary changes in recent decades. The advent of the cancer stem cell theory has accelerated our understanding of the cancer cell. However, there is increasing evidence that cancer cells are influenced by their surrounding microenvironment. PURPOSE: This review divides the tumor microenvironment into four functional components-the stem cell niche, cancer stroma, immune cells, and vascular endothelia-and examines their individual and collective influence on the growth and metastasis of the colon cancer stem cell. The discussion will highlight the need to fully exploit the tumor microenvironment when designing future prognostic tools and therapies.

Chen, W., et al. (2016). "Cancer Stem Cell Quiescence and Plasticity as Major Challenges in Cancer Therapy." Stem Cells Int **2016**: 1740936.

Cells with stem-like properties, tumorigenic potential, and treatment-resistant phenotypes have been identified in many human malignancies. Based on the properties they share with nonneoplastic stem cells or their ability to initiate and propagate tumors in vivo, such cells were designated as cancer stem (stem-like) or tumor initiating/propagating cells. Owing to their implication in treatment resistance, cancer stem cells (CSCs) have been the subject of intense investigation in past years. Comprehension of CSCs' intrinsic properties and mechanisms they develop to survive and even enhance their aggressive phenotype within the hostile conditions of the tumor microenvironment has reoriented therapeutic strategies to fight cancer. This report provides selected examples of malignancies in which the presence of CSCs has been evidenced and briefly discusses methods to identify, isolate, and functionally characterize the CSC subpopulation of cancer cells. Relevant biological targets in CSCs, their link to treatment resistance, proposed targeting strategies, and limitations of these approaches are presented. Two major aspects of CSC physiopathology, namely, relative in vivo quiescence and plasticity in response to microenvironmental cues or treatment, are highlighted. Implications of these

findings in the context of the development of new therapies are discussed.

Cheng, Y. C., et al. (2013). "Paclitaxel and Trastuzumab as Maintenance Therapy in Patients with HER2-Positive Metastatic Breast Cancer Who Underwent High-Dose Chemotherapy and Autologous Hematopoietic Stem Cell Transplantation." J Cancer **4**(8): 679-685.

We examined the feasibility and safety of using paclitaxel and trastuzumab as maintenance therapy after high-dose chemotherapy (HDC) with autologous hematopoietic stem cell transplantation (AHST) for patients with HER2-positive metastatic breast cancer. Ten patients (9 women and 1 man) were enrolled in the study. The median age was 46.5 years (range, 27-65 years). The median follow-up time was 1003 days (range, 216-2526 days). All patients had metastatic disease, but 2 had only bone metastasis. One patient had complete response, 6 had partial response and 3 had stable disease to the standard-dose chemotherapy prior to transplantation. The conditioning regimen consisted of cyclophosphamide, carmustine, and thiotepa. After AHST, patients received weekly paclitaxel for 12 doses and trastuzumab every 3 weeks for 1 year as maintenance therapy. All patients experienced successful engraftment. The only grade 4 toxic effects observed were leukopenia and thrombocytopenia. The most common grade 3 toxic effect was neutropenic fever. No treatment-related deaths were observed. The median progression-free survival time was 441 days, and the median overall survival time was 955 days. Two patients died in accidents while their disease remained in remission. Five patients died with disease progression. At the time of this report, 3 patients are alive with stable disease, 1 of whom has remained free of disease progression for 2526 days since transplantation. Our findings indicate that paclitaxel plus trastuzumab as maintenance therapy after HDC with AHST for patients with HER2-positive metastatic breast cancer not only is feasible and safe but also results in survival outcomes similar to historical results.

Cheng, Y. C., et al. (2004). "The use of high-dose cyclophosphamide, carmustine, and thiotepa plus autologous hematopoietic stem cell transplantation as consolidation therapy for high-risk primary breast cancer after primary surgery or neoadjuvant chemotherapy." Biol Blood Marrow Transplant **10**(11): 794-804.

We assessed the 5-year results of a high-dose cyclophosphamide, carmustine, and thiotepa (CBT) regimen plus autologous hematopoietic stem cell transplantation (AHST) as an adjuvant consolidation therapy for high-risk primary breast cancer patients with > or =10 positive axillary lymph nodes after primary surgery or > or =4 positive axillary lymph nodes after neoadjuvant chemotherapy and surgery. The associations of various potential prognostic factors with the relapse-free survival (RFS) rate and overall survival (OS) rate were determined. Between October 1992 and March 2000, 177 eligible patients (median age, 46 years) were given high-dose CBT followed by AHST. At a median follow-up of 63 months, the acute treatment-related mortality was 4.5%. Estimated 5-year RFS and OS rates were 62% and 68%, respectively, for all patients. For patients with > or =10 positive axillary lymph nodes after primary surgery, the 5-year RFS and OS rates were 71% and 70%, respectively, and for patients with > or =4 positive axillary lymph nodes after neoadjuvant chemotherapy, the 5-year RFS and OS rates were 53% and 66%, respectively. In 2-sided log-rank tests, earlier disease stage, a lower lymph node ratio, and a lower tumor score were associated with a prolonged RFS and OS. In a multivariate proportional hazards model, disease stage and lymph node ratio remained significant. We concluded that high-dose CBT with AHST for high-risk primary breast cancer is feasible, with comparable efficacy to other phase II studies. More than a 50% estimated 5-year survival rate was seen in all high-risk primary breast cancer patients. In accordance with results from recent randomized studies, we need to continue high-dose chemotherapy with AHST for patients with high-risk primary breast cancer in the phase III randomized setting.

Cihova, M., et al. (2011). "Stem cell based cancer gene therapy." Mol Pharm **8**(5): 1480-1487.

The attractiveness of prodrug cancer gene therapy by stem cells targeted to tumors lies in activating the prodrug directly within the tumor mass, thus avoiding systemic toxicity. Suicide gene therapy using genetically engineered mesenchymal stem cells has the advantage of being safe, because prodrug administration not only eliminates tumor cells but consequently kills the more resistant therapeutic stem cells as well. This review provides an explanation of the stem cell-targeted prodrug cancer gene therapy principle, with focus on the choice of prodrug, properties of bone marrow and adipose tissue-derived mesenchymal stem and neural stem cells as well as the mechanisms of their tumor homing ability. Therapeutic achievements of the cytosine deaminase/5-fluorocytosine prodrug system and Herpes simplex virus thymidine kinase/ganciclovir are discussed. In addition, delivery of immunostimulatory cytokines, apoptosis inducing genes, nanoparticles and antiangiogenic proteins by stem cells to tumors and metastases is discussed as a promising approach for antitumor therapy. Combinations of traditional,

targeted and stem cell-directed gene therapy could significantly advance the treatment of cancer.

Clay, T. M., et al. (1999). "Potential use of T cell receptor genes to modify hematopoietic stem cells for the gene therapy of cancer." Pathol Oncol Res **5**(1): 3-15.

The purpose of this review is to illustrate some of the technical and biological hurdles that need to be addressed when developing new gene therapy based clinical trials. Gene transfer approaches can be used to "mark" cells to monitor their persistence in vivo in patients, to protect cells from toxic chemotherapeutic agents, correct a genetic defect within the target cell, or to confer a novel function on the target cell. Selection of the most suitable vector for gene transfer depends upon a number of factors such as the target cell itself and whether gene expression needs to be sustained or transient. The TCR gene transfer approach described here represents one innovative strategy being pursued as a potential therapy for metastatic melanoma. Tumor reactive T cells can be isolated from the tumor infiltrating lymphocytes (TIL) of melanoma patients. A retroviral vector has been constructed containing the T cell receptor (TCR) alpha and beta chain genes from a MART-1-specific T cell clone (TIL 5). Jurkat cells transduced with this virus specifically release cytokine in response to MART-1 peptide pulsed T2 cells, showing that the virus can mediate expression of a functional TCR. HLA-A2 transgenic mice are being used to examine whether transduced bone marrow progenitor cells will differentiate in vivo into mature CD8+ T cells expressing the MART-1-specific TCR. Expression of the human TCR alpha and beta chain genes has been detected by RT-PCR in the peripheral blood of HLA-A2 transgenic mice reconstituted with transduced mouse bone marrow. Expression of the TIL 5 TCR genes in the peripheral blood of these mice was maintained for greater than 40 weeks after bone marrow reconstitution. TIL 5 TCR gene expression was also maintained following transfer of bone marrow from mice previously reconstituted with transduced bone marrow to secondary mouse recipients, suggesting that a pluripotent progenitor or lymphocyte progenitor cell has been transduced.

Clement, F., et al. (2017). "Stem cell manipulation, gene therapy and the risk of cancer stem cell emergence." Stem Cell Investig **4**: 67.

Stem cells (SCs) have been extensively studied in the context of regenerative medicine. Human hematopoietic stem cell (HSC)-based therapies have been applied to treat leukemic patients for decades. Handling of mesenchymal stem cells (MSCs) has also raised hopes and concerns in the field of tissue engineering. Lately, discovery of cell reprogramming by Yamanaka's team has profoundly modified research strategies and approaches in this domain. As we gain further insight into cell fate mechanisms and identification of key actors and parameters, this also raises issues as to the manipulation of SCs. These include the engraftment of manipulated cells and the potential predisposition of those cells to develop cancer. As a unique and pioneer model, the use of HSCs to provide new perspectives in the field of regenerative and curative medicine will be reviewed. We will also discuss the potential use of various SCs from embryonic to adult stem cells (ASCs), including induced pluripotent stem cells (iPSCs) as well as MSCs. Furthermore, to sensitize clinicians and researchers to unresolved issues in these new therapeutic approaches, we will highlight the risks associated with the manipulation of human SCs from embryonic or adult origins for each strategy presented.

Coombes, R. C., et al. (2005). "High dose chemotherapy and autologous stem cell transplantation as adjuvant therapy for primary breast cancer patients with four or more lymph nodes involved: long-term results of an international randomised trial." Ann Oncol **16**(5): 726-734.

BACKGROUND: The purpose of this study was to assess whether a short course of anthracycline containing chemotherapy followed by high dose therapy with autologous stem-cell support improves disease-free and overall survival as compared with conventional, anthracycline containing chemotherapy, in patients with primary breast cancer and four or more histologically involved lymph nodes. PATIENTS AND METHODS: Two hundred and eighty one patients entered into a randomised clinical trial were allocated to receive standard, conventional treatment (5-fluorouracil, epirubicin and cyclophosphamide-FEC for six cycles) or FEC for three cycles followed by high dose therapy consisting of cyclophosphamide, thiotepa and carboplatin and stem cell rescue (HDT). To be eligible, patients had to be free of overt metastatic disease and be < or =60 years of age. Analyses were according to intention to treat. RESULTS: At a median follow up of 68 months, 118 patients have experienced a relapse or death from breast cancer (62 in the FEC followed by HDT arm and 56 in the conventional FEC arm) and a total of 100 patients have died (54 in the FEC followed by HDT arm and 46 in the conventional FEC arm). No significant difference was observed in relapse-free survival [hazard ratio 1.06, 95% CI 0.74-1.52, p = 0.76] or overall survival [hazard ratio 1.18, 95% CI 0.80-1.75, p = 0.40]. Five patients died from treatment related causes, three as a consequence of HDT and two in the conventional FEC arm. CONCLUSIONS: At the

present time, no benefit has been observed from replacing three cycles of conventional chemotherapy with the HDT regimen described here. Patients should continue to receive conventional chemotherapy as adjuvant therapy for breast cancer.

Costea, D. E., et al. (2006). "Cancer stem cells - new and potentially important targets for the therapy of oral squamous cell carcinoma." Oral Dis **12**(5): 443-454.

There is increasing evidence that the growth and spread of cancers is driven by a small subpopulation of cancer stem cells (CSCs) - the only cells that are capable of long-term self-renewal and generation of the phenotypically diverse tumour cell population. Current failure of cancer therapies may be due to their lesser effect on potentially quiescent CSCs which remain vital and retain their full capacity to repopulate the tumour. Treatment strategies for the elimination of cancer therefore need to consider the consequences of the presence of CSCs. However, the development of new CSC-targeted strategies is currently hindered by the lack of reliable markers for the identification of CSCs and the poor understanding of their behaviour and fate determinants. Recent studies of cell lines derived from oral squamous cell carcinoma (OSCC) indicate the presence of subpopulations of cells with phenotypic and behavioural characteristics corresponding to both normal epithelial stem cells and to cells capable of initiating tumours in vivo. The present review discusses the relevance to OSCC of current CSC concepts, the state of various methods for CSC identification, characterization and isolation (clonal functional assay, cell sorting based on surface markers or uptake of Hoechst dye), and possible new approaches to therapy.

Couriel, D. R., et al. (2000). "Role of tumor necrosis factor-alpha inhibition with infliximAB in cancer therapy and hematopoietic stem cell transplantation." Curr Opin Oncol **12**(6): 582-587.

Tumor necrosis factor (TNF)-alpha is a central cytotoxic and proinflammatory cytokine. Research on the benefits of TNF-alpha inhibition as a form of therapy has focused almost exclusively on autoimmune, inflammatory disorders. InfliximAB, a chimeric antibody to human TNF-alpha, was recently approved for the management of Crohn disease and rheumatoid arthritis. The potential applications of infliximAB in the management of cancer are just beginning to be explored. This article reviews the biology, mechanism of action, pharmacology, and toxicity of infliximAB. Existing clinical experience and infliximAB's potential role as an immunosuppressant and antitumor agent in the management of cancer are also discussed.

De Angelis, M. L., et al. (2016). "Cancer Stem Cell-Based Models of Colorectal Cancer Reveal Molecular Determinants of Therapy Resistance." Stem Cells Transl Med **5**(4): 511-523.

UNLABELLED: Colorectal cancer (CRC) therapy mainly relies on the use of conventional chemotherapeutic drugs combined, in a subset of patients, with epidermal growth factor receptor [EGFR]-targeting agents. Although CRC is considered a prototype of a cancer stem cell (CSC)-driven tumor, the effects of both conventional and targeted therapies on the CSC compartment are largely unknown. We have optimized a protocol for colorectal CSC isolation that allowed us to obtain CSC-enriched cultures from primary tumor specimens, with high efficiency. CSC isolation was followed by in vitro and in vivo validation, genetic characterization, and drug sensitivity analysis, thus generating panels of CSC lines with defined patterns of genetic mutations and therapy sensitivity. Colorectal CSC lines were polyclonal and maintained intratumor heterogeneity in terms of somatically acquired mutations and differentiation state. Such CSC-enriched cultures were used to investigate the effects of both conventional and targeted therapies on the CSC compartment in vivo and to generate a proteomic picture of signaling pathways implicated in sensitivity/resistance to anti-EGFR agents. We propose CSC lines as a sound preclinical framework to test the effects of therapies in vitro and in vivo and to identify novel determinants of therapy resistance. SIGNIFICANCE: Colorectal cancer stem cells (CSCs) have been shown to be responsible for tumor propagation, metastatic dissemination, and relapse. However, molecular pathways present in CSCs, as well as mechanisms of therapy resistance, are mostly unknown. Taking advantage of genetically characterized CSC lines derived from colorectal tumors, this study provides an extensive analysis of CSC response to EGFR-targeted therapy in vivo and an overview of factors implicated in therapy response or resistance. Furthermore, the implementation of a biobank of molecularly annotated CSC lines provides an innovative resource for future investigations in colorectal cancer.

deMagalhaes-Silverman, M., et al. (1997). "High-dose chemotherapy and autologous stem cell support followed by posttransplantation doxorubicin as initial therapy for metastatic breast cancer." Clin Cancer Res **3**(2): 193-197.

High-dose chemotherapy is associated with a high complete response rate and possibly some survival advantage in patients with metastatic breast cancer. We designed a clinical trial consisting of a two-step high-dose chemotherapy regimen followed

by posttransplantation doxorubicin as the first chemotherapy treatment for metastatic disease. Twenty-one patients with metastatic breast cancer and no previous chemotherapy for metastatic disease were treated with high-dose cyclophosphamide (Cy; 5000 mg/m2), followed by granulocyte colony-stimulating factor. Peripheral blood stem cells were collected. Subsequently, patients received Cy (6000 mg/m2), thiotepa (500 mg/m2), and carboplatin (800 mg/m2) (CTCb) with hematopoietic rescue. Upon recovery of hematopoietic and gastrointestinal toxicity, three cycles of doxorubicin (Dox; 60 mg/m2) were delivered. After Cy, nine patients (45%) developed neutropenic fevers. There were no episodes of bacteremia. Patients received CTCb 37 days after starting Cy and had a hospital stay of 19 days. After CTCb, the median number of days to an absolute neutrophil count >5 x 10(9)/liter was 8, and the median number of days to a platelet count >20 x 10(9)/liter was 9. Neutropenic fevers occurred in 12 patients. There were no hemorrhagic complications. Fifty-five of the 63 planned courses of Dox were delivered. The median time from peripheral blood stem cell infusion to the first Dox cycle was 38 days. The median time to the second Dox cycle was 28 days, and to the last cycle was 30 days. Three episodes of neutropenic fevers were observed. Two patients developed herpes zoster. This regimen is feasible, with acceptable toxicity.

deMagalhaes-Silverman, M., et al. (1998). "High-dose chemotherapy and autologous stem cell support followed by post-transplant doxorubicin and taxol as initial therapy for metastatic breast cancer: hematopoietic tolerance and efficacy." Bone Marrow Transplant **21**(12): 1207-1211.

A multistep HDC regimen was designed as first-line chemotherapy for MBC. Twenty-four patients with MBC and no previous chemotherapy for metastatic disease were treated with high-dose cyclophosphamide (5000 mg/m2), and etoposide (1000 mg/m2) (CyVP16), followed by granulocyte colony-stimulating factor (G-CSF). Peripheral blood stem cells (PBSCs) were collected. Subsequently patients received cyclophosphamide (6000 mg/m2), thiotepa (500 mg/m2) and carboplatin (800 mg/m2) (CTCb) with hematopoietic rescue. Upon recovery from hematopoietic and gastrointestinal toxicity three cycles of doxorubicin (50 mg/m2) and taxol (150 mg/m2) were delivered. After CyVP16 42% of patients developed neutropenic fevers. There was one documented episode of bacteremia. Patients received CTCb 32 days after starting CyVP16. After CTCb the median number of days to ANC >5 x 10(9)/l was 10 and to a platelet count >20 x 10(9)/l was 14. Neutropenic fevers developed in 16 patients. There were no hemorrhagic episodes. A total of 69 cycles of doxorubicin and taxol were delivered (87% of planned). The median time from PBSC infusion to the first cycle was 38 days. The median time to the second cycle was 27 days and to the last cycle was 24 days. One patient developed congestive heart failure. Two episodes of neutropenic fevers were observed. No toxicity-related deaths were observed. Grafts are stable at 6 months post transplantation. This multistep regimen is feasible with acceptable toxicity.

Demirkazik, A., et al. (2002). "Effect of prior therapy and bone marrow metastases on progenitor cell content of blood stem cell harvests in breast cancer patients." Biol Blood Marrow Transplant **8**(5): 268-272.

This study was designed to examine the relationship of prior therapy, bone marrow metastases, mobilization, and blood progenitor/stem cell (BSC) collection in breast cancer patients. Cells were collected from 19 breast cancer patients during steady state (nonmobilized group) and from 69 breast cancer patients after cytokine administration (mobilized group). Characteristics of the patients were compared with the cells obtained. A significant inverse association was found between the number of chemotherapy regimens the patients had received prior to BSC collection and the mononuclear cell (MNC) count of the product per liter of blood processed (LBP) with apheresis (P =.0006) and the granulocyte monocyte/macrophage colony-forming cell (GM-CFC) numbers per LBP (P =.0002). This association was evident in both mobilized and nonmobilized patients. Similar results were seen in those 25 patients who had received prior radiation therapy (MNC/LBP, P =.0003; GM-CFC/LBP, P =.0004). Patients in both the mobilized and nonmobilized groups with marrow metastases at the time of collection also had significantly lower levels of MNC/LBP (P =.0039) and GM-CFC/LBP (P =.0001) than did those without marrow metastases. The findings suggest that prior administration of radiation therapy and/or chemotherapy and the presence of marrow metastases all negatively impacted the collection of mobilized and nonmobilized progenitor cells from breast cancer patients. The mechanisms of this impact are not understood.

Deng, Z., et al. (2015). "Adoptive T-cell therapy of prostate cancer targeting the cancer stem cell antigen EpCAM." BMC Immunol **16**: 1.

BACKGROUND: Adoptive transfer of tumor infiltrating or circulating lymphocytes transduced with tumor antigen receptors has been examined in various clinical trials to treat human cancers. The tumor antigens targeted by transferred lymphocytes affects the efficacy of this therapeutic approach. Because

cancer stem cells (CSCs) play an important role in tumor growth and metastasis, we hypothesized that adoptive transfer of T cells targeting a CSC antigen could result in dramatic anti-tumor effects. RESULTS: An EpCAM-specific chimeric antigen receptor (CAR) was constructed to transduce human peripheral blood lymphocytes (PBLs) and thereby enable them to target the CSC marker EpCAM. To investigate the therapeutic capabilities of PBLs expressing EpCAM-specific CARs, we used two different tumor models, PC3, the human prostate cancer cell line, which has low expression levels of EpCAM, and PC3M, a highly metastatic clone of PC3 that has high expression levels of EpCAM. We demonstrate that CAR-expressing PBLs can kill PC3M tumor cells in vitro and in vivo. Despite the low expression of EpCAM on PC3 cells, CAR-expressing PBLs significantly inhibited tumor growth and prolonged mouse survival in a PC3 metastasis model, probably by targeting the highly proliferative and metastatic population of cancer cells. CONCLUSIONS: Our data demonstrate that PBLs expressing with EpCAM-specific CARs have significant anti-tumor activity against prostate cancer. Therefore, the adoptive transfer of T cells targeting EpCAM could have great potential as a cancer treatment.

Deshmukh, A., et al. (2016). "Cancer stem cell metabolism: a potential target for cancer therapy." Mol Cancer **15**(1): 69.

Cancer Stem cells (CSCs) are a unipotent cell population present within the tumour cell mass. CSCs are known to be highly chemo-resistant, and in recent years, they have gained intense interest as key tumour initiating cells that may also play an integral role in tumour recurrence following chemotherapy. Cancer cells have the ability to alter their metabolism in order to fulfil bio-energetic and biosynthetic requirements. They are largely dependent on aerobic glycolysis for their energy production and also are associated with increased fatty acid synthesis and increased rates of glutamine utilisation. Emerging evidence has shown that therapeutic resistance to cancer treatment may arise due to dysregulation in glucose metabolism, fatty acid synthesis, and glutaminolysis. To propagate their lethal effects and maintain survival, tumour cells alter their metabolic requirements to ensure optimal nutrient use for their survival, evasion from host immune attack, and proliferation. It is now evident that cancer cells metabolise glutamine to grow rapidly because it provides the metabolic stimulus for required energy and precursors for synthesis of proteins, lipids, and nucleic acids. It can also regulate the activities of some of the signalling pathways that control the proliferation of cancer cells.This review describes the key metabolic pathways required by CSCs to maintain a survival advantage and highlights how a combined approach of targeting cellular metabolism in conjunction with the use of chemotherapeutic drugs may provide a promising strategy to overcome therapeutic resistance and therefore aid in cancer therapy.

Ding, X. W., et al. (2010). "ABCG2: a potential marker of stem cells and novel target in stem cell and cancer therapy." Life Sci **86**(17-18): 631-637.

ABCG2 is a member of the ATP binding cassette (ABC) transporters, which can pump a wide variety of endogenous and exogenous compounds out of cells. Widely expressed in stem cells, ABCG2 is also found to confer the side population phenotype and is recognized as a universal marker of stem cells. Although the precise physiological role of ABCG2 in stem cells is still unclear, existing data strongly suggest that ABCG2 plays an important role in promoting stem cell proliferation and the maintenance of the stem cell phenotype. In addition, ABCG2 is also found to be expressed in a number of cancer cells and appears to be a marker of cancer stem cells. Moreover, ABCG2 expression in tumors may contribute to their formation and progression. Thus, ABCG2 has potential applications in stem cell and tumor therapy.

Donahue, T. R. and D. W. Dawson (2011). "Nodal/Activin signaling: a novel target for pancreatic cancer stem cell therapy." Cell Stem Cell **9**(5): 383-384.

Targeting of cancer stem cells (CSCs) has the potential to address the recalcitrance of pancreatic cancer to chemotherapy. In this issue of Cell Stem Cell, Lonardo et al. (2011) demonstrate that Nodal/Activin signaling is crucial for the maintenance and tumor-initiating capacity of pancreatic CSCs.

Donnenberg, V. S. and A. D. Donnenberg (2015). "Stem cell state and the epithelial-to-mesenchymal transition: Implications for cancer therapy." J Clin Pharmacol **55**(6): 603-619.

The cancer stem cell paradigm, the epithelial-to-mesenchymal transition and its converse, the mesenchymal-to-epithelial transition, have reached convergence. Implicit in this understanding is the notion that cancer cells can change state, and with such change come bidirectional alterations in motility, proliferative activity, and drug resistance. As such, tumors present a moving target for antineoplastic therapy. This article will review the evolving adult stem cell paradigm and how changes in our understanding of the bidirectional nature of cancer cell differentiation may affect the selection and timing of antineoplastic therapy. The goal is to determine how to best administer therapies potentially targeted against

the cancer stem cell state in the context of established treatment regimens, and to evaluate long-term effects beyond tumor regression.

Dwyer, R. M., et al. (2010). "Advances in mesenchymal stem cell-mediated gene therapy for cancer." Stem Cell Res Ther **1**(3): 25.

Mesenchymal stem cells have a natural tropism for tumours and their metastases, and are also considered immunoprivileged. This remarkable combination of properties has formed the basis for many studies investigating their potential as tumour-specific delivery vehicles for suicide genes, oncolytic viruses and secreted therapeutic proteins. The aim of the present review is to discuss the range of approaches that have been used to exploit the tumour-homing capacity of mesenchymal stem cells for gene delivery, and to highlight advances required to realize the full potential of this promising approach.

Elias, A. D., et al. (1993). "High-dose combined alkylating agent therapy with autologous stem cell support and chest radiotherapy for limited small-cell lung cancer." Chest **103**(4 Suppl): 433S-435S.

Although initially responsive to chemotherapy, patients with small-cell lung cancer (SCLC) almost invariably suffer relapse. Recurrent SCLC responds poorly to treatment. Previous trials using high-dose chemotherapy with bone marrow support have commonly used single agents or combined alkylating agents without chest radiotherapy. Among patients with limited disease receiving dose-intensive chemotherapy, locoregional relapse remained the predominant site of first failure. Recent phase II trials using intensive locoregional therapy (aggressive concurrent chemoradiotherapy) have resulted in promising survival. Our trial used combined alkylating agents with autologous marrow support and chest radiotherapy in patients with limited disease in response to conventional-dose induction chemotherapy. Of 19 patients treated, the actuarial survival was 56% with a median follow-up of 18 months following high-dose therapy. Patients who achieved complete or near-complete response prior to high-dose therapy enjoyed the best prognosis. Continued evaluation of intensive systemic and local therapy for SCLC is indicated.

Eltoukhy, H. S., et al. (2018). "Immune modulation by a cellular network of mesenchymal stem cells and breast cancer cell subsets: Implication for cancer therapy." Cell Immunol **326**: 33-41.

The immune modulatory properties of mesenchymal stem cells (MSCs) are mostly controlled by the particular microenvironment. Cancer stem cells (CSCs), which can initiate a clinical tumor, have been the subject of intense research. This review article discusses investigative studies of the roles of MSCs on cancer biology including on CSCs, and the potential as drug delivery to tumors. An understanding of how MSCs behave in the tumor microenvironment to facilitate the survival of tumor cells would be crucial to identify drug targets. More importantly, since CSCs survive for decades in dormancy for later resurgence, studies are presented to show how MSCs could be involved in maintaining dormancy. Although the mechanism by which CSCs survive is complex, this article focus on the cellular involvement of MSCs with regard to immune responses. We discuss the immunomodulatory mechanisms of MSC-CSC interaction in the context of therapeutic outcomes in oncology. We also discuss immunotherapy as a potential to circumventing this immune modulation.

Fabian, A., et al. (2013). "The hitchhikers guide to cancer stem cell theory: markers, pathways and therapy." Cytometry A **83**(1): 62-71.

Cancer stem cell (CSC) biology is a rapidly developing field within cancer research. CSCs are postulated to be a unique cell population exclusively capable of infinite self renewal, multilineage differentiation and with ability to evade conventional cytotoxic cancer therapy. These traits distinguish CSCs from their more differentiated counterparts, which possess only limited or no potential for self renewal and tumor initiation. Therefore, CSCs would be the driving motor of malignant growth and therapy resistance. Accordingly, successful cancer treatment would need to eliminate this highly potent group of cells, since even small residual numbers would suffice to recapitulate the disease after therapy. Putative CSCs has been identified in a broad range of human malignancies and several cell surface markers have been associated with their stem cell phenotype. Despite all efforts, a pure CSC population has not been isolated and often in vitro clonogenic and in vivo tumorigenic potential is found in several cell populations with occasionally contradictory surface marker signatures. Here, we give a brief overview of recent advances in CSC theory, including the signaling pathways in CSCs that also appear crucial for stem cells homeostasis in normal tissues. We discuss evidence for the interaction of CSCs with the stromal tumor environment. Finally, we review the emerging potentially effective CSC-targeted treatment strategies and their future role in therapy.

Fouse, S. D., et al. (2014). "Response of primary glioblastoma cells to therapy is patient specific and independent of cancer stem cell phenotype." Neuro Oncol **16**(3): 361-371.

BACKGROUND: Glioblastoma multiforme (GBM) contains a population of cells that exhibit stem

cell phenotypes. These cancer stem cells (CSCs) may be a source of therapeutic resistance, although support for this important concept is limited. METHODS: We determined whether early-passage GBM CSCs respond differently than patient-matched, genotypically similar non-CSCs to clinically relevant single or serial doses of temozolomide (TMZ), radiation therapy (XRT), or alternating TMZ treatment and XRT, which is the standard of care for GBM patients. RESULTS: Despite the phenotypic differences, including the presence of stem cell markers and formation of intracranial tumors, the CSCs and matched non-CSCs were equally resistant to TMZ in a majority of patients, using 2 independent assays. TMZ response was consistent with methylated O (6)-DNA methylguanine-methyltransferase (MGMT) and MGMT protein levels in both culture types. In contrast, CSCs were unexpectedly more responsive to XRT compared with matched non-CSCs from 2 patients despite having relatively equal resistance to TMZ. However, for the majority of culture pairs from individual patients, responses in CSCs were indistinguishable from non-CSC cultures. CONCLUSIONS: In our patient-matched primary cultures, response to TMZ was tightly linked to the individual tumor's MGMT status and independent of their phenotypic differences. TMZ and XRT together revealed no additive benefit compared with monotherapy for either culture type, in contrast to the notion that the CSC population is more resistant to XRT. If the tumor cell response in vitro mirrors therapeutic response in larger patient cohorts, these rapid assays in primary cultures could allow -empirical selection of efficacious therapeutic agents on a patient-specific basis.

Gasch, C., et al. (2017). "Catching moving targets: cancer stem cell hierarchies, therapy-resistance & considerations for clinical intervention." Mol Cancer **16**(1): 43.

It is widely believed that targeting the tumour-initiating cancer stem cell (CSC) component of malignancy has great therapeutic potential, particularly in therapy-resistant disease. However, despite concerted efforts, CSC-targeting strategies have not been efficiently translated to the clinic. This is partly due to our incomplete understanding of the mechanisms underlying CSC therapy-resistance. In particular, the relationship between therapy-resistance and the organisation of CSCs as Stem-Progenitor-Differentiated cell hierarchies has not been widely studied. In this review we argue that modern clinical strategies should appreciate that the CSC hierarchy is a dynamic target that contains sensitive and resistant components and expresses a collection of therapy-resisting mechanisms. We propose that the CSC hierarchy at primary presentation changes in response to clinical intervention, resulting in a recurrent malignancy that should be targeted differently. As such, addressing the hierarchical organisation of CSCs into our bench-side theory should expedite translation of CSC-targeting to bed-side practice. In conclusion, we discuss strategies through which we can catch these moving clinical targets to specifically compromise therapy-resistant disease.

Gholizadeh-Ghaleh Aziz, S., et al. (2017). "An update clinical application of amniotic fluid-derived stem cells (AFSCs) in cancer cell therapy and tissue engineering." Artif Cells Nanomed Biotechnol **45**(4): 765-774.

Recent studies have elucidated that cell-based therapies are promising for cancer treatments. The human amniotic fluid stem (AFS) cells are advantageous cells for such therapeutic schemes that can be innately changed to express therapeutic proteins. HAFSCs display a natural tropism to cancer cells in vivo. They can be useful in cancer cells targeting. Moreover, they are easily available from surplus diagnostic samples during pregnancy and less ethical and legal concern are associated with the collection and application than other putative cells are subjected. This review will designate representatives of amniotic fluid and stem cell derived from amniotic fluid. For this propose, we collect state of human AFS cells data applicable in cancer therapy by dividing this approach into two main classes (nonengineered and engineered based approaches). Our study shows the advantage of AFS cells over other putative cells types in terms differentiation ability to a wide range of cells by potential and effective use in preclinical studies for a variety of diseases. This study has shown the elasticity of human AFS cells and their favorable potential as a multipotent cell source for regenerative stem cell therapy and capable of giving rise to multiple lineages including such as osteoblasts and adipocyte.

Ghotra, V. P., et al. (2009). "The cancer stem cell microenvironment and anti-cancer therapy." Int J Radiat Biol **85**(11): 955-962.

PURPOSE: Tumours are composed of a heterogeneous cell population. Cancer stem cells, which make up a minor fraction of a tumour, may be the cells that initiate and sustain tumour growth. Cancer stem cells are believed to share many properties with normal stem cells that render them relatively insensitive to classical radio- and chemotherapy. CONCLUSIONS: We discuss what those (cancer) stem cell properties are and how the interactions with the microenvironment--'the niche'--control those aspects of (cancer) stem cell biology. We

also describe possible strategies to target cancer stem cells in order to prevent cancers from escaping therapy.

Giulino-Roth, L., et al. (2018). "Outcome of children and adolescents with relapsed Hodgkin lymphoma treated with high-dose therapy and autologous stem cell transplantation: the Memorial Sloan Kettering Cancer Center experience." Leuk Lymphoma **59**(8): 1861-1870.

To evaluate outcomes and prognostic markers among children with relapsed Hodgkin lymphoma (HL) treated with autologous stem cell transplant (ASCT), we conducted a retrospective analysis of 36 consecutive pediatric patients treated at Memorial Sloan Kettering Cancer Center from 1989 to 2013. With a median follow-up of 9.6 years, the 10-year overall survival (OS) and event-free survival (EFS) were 74.1 and 67.1% respectively. Absence of B-symptoms, chemotherapy-sensitive disease, and transplant date after 1997 were each associated with superior EFS [HR 0.12 (p =.0015), 0.18 (p =.0039), and 0.17 (p =.0208), respectively]. Childhood Hodgkin International Prognostic Score at relapse (R-CHIPS) was calculated in a subset of patients (n = 22) and a lower score was associated with improved OS (HR 0.29, p =.0352) and a trend toward improved EFS (HR 0.38, p =.0527). In summary, ASCT results in durable remission for the majority of pediatric patients with relapsed HL. R-CHIPS should be evaluated in larger cohorts as a potential predictive tool.

Gordeeva, O. (2018). "Cancer-testis antigens: Unique cancer stem cell biomarkers and targets for cancer therapy." Semin Cancer Biol.

Cancer-testis antigens (CTAs) are considered as unique and promising cancer biomarkers and targets for cancer therapy. CTAs are multifunctional protein group with specific expression patterns in normal embryonic and adult cells and various types of cancer cells. CTAs are involved in regulating of the basic cellular processes during development, stem cell differentiation and carcinogenesis though the biological roles and cell functions of CTA families remain largely unclear. Analysis of CTA expression patterns in embryonic germ and somatic cells, pluripotent and multipotent stem cells, cancer stem cells and their cell descendants indicates that rearrangements of characteristic CTA profiles (aberrant expression) could be associated with cancer transformation and failure of the developmental program of cell lineage specification and germ line restriction. Therefore, aberrant CTA profiles can be used as panels of biomarkers for diagnoses and the selection of cancer treatment strategies. Moreover, immunogenic CTAs are prospective targets for cancer immunotherapy. Clinical trials testing broad range of cancer therapeutic vaccines against antigens of MAGEA and NY-ESO-1 families for treating various cancers have shown mixed clinical efficiency, safety and tolerability, suggesting the requirement of in-depth research of CTA expression in normal and cancer stem cells and extensive clinical trials for improving cancer immunotherapy technologies. This review focuses on recent advancement in study of CTAs in normal and cancer cells, particularly in normal and cancer stem cells, and provides a new insight into CTA expression patterns during normal and cancer stem cell lineage development. Additionally, new approaches in development of effective CTA-based therapies exclusively targeting cancer stem cells will be discussed.

Gruber, W., et al. (2017). "Understanding cell signaling in cancer stem cells for targeted therapy - can phosphoproteomics help to reveal the secrets?" Cell Commun Signal **15**(1): 12.

BACKGROUND: Cancer represents heterogeneous and aberrantly proliferative manifestations composed of (epi)genetically and phenotypically distinct cells with a common clonal origin. Cancer stem cells (CSC) make up a rare subpopulation with the remarkable capacity to initiate, propagate and spread a malignant disease. Furthermore, CSC show increased therapy resistance, thereby contributing to disease relapse. Elimination of CSC, therefore, is a crucial aim to design efficacious treatments for long-term survival of cancer patients. In this article, we highlight the nature of CSC and propose that phosphoproteomics based on unbiased high-performance liquid chromatography-mass spectrometry provides a powerful tool to decipher the molecular CSC programs. Detailed knowledge about the regulation of signaling processes in CSC is a prerequisite for the development of patient-tailored multi-modal treatments including the elimination of rare CSC. MAIN BODY: Phosphorylation is a crucial post-translational modification regulating a plethora of both intra- and intercellular communication processes in normal and malignant cells. Small-molecule targeting of kinases has proven successful in the therapy, but the high rates of relapse and failure to stem malignant spread suggest that these kinase inhibitors largely spare CSC. Studying the kinetics of global phosphorylation patterns in an unbiased manner is, therefore, required to improve strategies and successful treatments within multi-modal therapeutic regimens by targeting the malignant behavior of CSC. The phosphoproteome comprises all phosphoproteins within a cell population that can be analyzed by phosphoproteomics, allowing the investigation of thousands of phosphorylation events. One major aspect is the perception of events underlying the

activation and deactivation of kinases and phosphatases in oncogenic signaling pathways. Thus, not only can this tool be harnessed to better understand cellular processes such as those controlling CSC, but also applied to identify novel drug targets for targeted anti-CSC therapy. CONCLUSION: State-of-the-art phosphoproteomics approaches focusing on single cell analysis have the potential to better understand oncogenic signaling in heterogeneous cell populations including rare, yet highly malignant CSC. By eliminating the influence of heterogeneity of populations, single-cell studies will reveal novel insights also into the inter- and intratumoral communication processes controlling malignant CSC and disease progression, laying the basis for improved rational combination treatments.

Haas, R., et al. (1997). "Tandem high-dose therapy with ifosfamide, epirubicin, carboplatin and peripheral blood stem cell support is an effective adjuvant treatment for high-risk primary breast cancer." Eur J Cancer **33**(3): 372-378.

We evaluated the therapeutic efficacy and toxicity of a tandem high-dose therapy with peripheral blood stem cell (PBSC) support in 40 patients with high-risk, primary breast cancer (stage II-III) and involvement of ten or more positive axillary lymph nodes. Their median age was 44 years (range 23-56). Two cycles of cytotoxic chemotherapy with ifosfamide (10000 mg/m2) and epirubicin (100 mg/m2) were administered. Granulocyte colony-stimulating factor (G-CSF) was given to hasten neutrophil reconstitution and to mobilise PBSC during marrow recovery. Leukaphereses were performed following the first and/or second cycle. Tandem high-dose therapy consisted of two cycles with ifosfamide (15 or 12 g/m2) and epirubicin (150 mg/m2), while carboplatin (900 mg/m2) was added for the last 24 patients included. Using an immunocytochemical method, two of 11 patients had cytokeratin-positive tumour cells in three leukapheresis products that were collected following the first G-CSF-supported cycle with ifosfamide and epirubicin, whereas only two harvests obtained following the second cycle in 26 patients contained cytokeratin-positive tumour cells. The number of CD34+ cells/kg re-infused following both high-dose cycles was similar (4.20 +/- 0.29 x 10(6), first cycle and 5.25 +/- 0.63 x 10(6), second cycle), and no notable difference was noted in the speed of haematological reconstitution. An absolute neutrophil count (ANC) of 0.5 x 10(9)/1 was reached after a median time of 13 days, while an unsupported platelet count of 20.0 x 10(9)/1 was achieved after a median time of 8 (first cycle) and 9 (second cycle) days post-transplantation. Patients autografted with more than 7.5 x 10(6) CD34+ cells/kg had platelet counts above 20 x 10(9)/1 within less than 10 days. 6 patients relapsed between 7 and 11 months (median 8 months) post-transplantation. 37 patients are alive and in remission with a median follow-up time of 11 months (range 1-38). This translates into a probability of disease-free survival (DFS) of 77% (95% CI 32-95%) at 38 months. The probability of overall survival is 85%, since 3 patients with local relapse achieved a second complete remission following surgery and involved-field radiotherapy. In conclusion, a sequential high-dose therapy including ifosfamide, epirubicin, carboplatin and PBSC support is well tolerated and effective in patients with high-risk primary breast cancer. Involved-field irradiation should be performed post-transplantation to reduce the risk of local relapse.

Haga, E., et al. (2014). "Therapy of peritoneally disseminated colon cancer by TAP-deficient embryonic stem cell-derived macrophages in allogeneic recipients." J Immunol **193**(4): 2024-2033.

We established a method to generate a large quantity of myeloid lineage cells from mouse embryonic stem (ES) cells, termed ES cell-derived proliferating myeloid cell lines (ES-ML). ES-ML continuously proliferated in the presence of M-CSF and GM-CSF. ES-ML genetically modified to express an anti-HER2 (neu) mAb single-chain V region fragment reduced the number of cocultured mouse Colon-26 cancer cells expressing HER2. Stimulation of ES-ML with IFN-gamma plus LPS or TNF resulted in almost complete killing of the Colon-26 cells by the ES-ML, and the cytotoxicity was mediated, in part, by NO produced by ES-ML. When ES-ML were injected into mice with i.p. established Colon-26 tumors, they efficiently infiltrated the tumor tissues. Injection of ES-ML with rIFN-gamma and LPS inhibited cancer progression in the mouse peritoneal cavity. Coinjection of TNF-transfected or untransfected ES-ML with rIFN-gamma inhibited cancer growth and resulted in prolonged survival of the treated mice. In this experiment, transporter associated with Ag processing (TAP)1-deficient ES-ML exhibited therapeutic activity in MHC-mismatched allogeneic recipient mice. Despite the proliferative capacity of ES-ML, malignancy never developed from the transferred ES-ML in the recipient mice. In summary, TAP-deficient ES-ML with anticancer properties exhibited a therapeutic effect in allogeneic recipients, suggesting the possible use of TAP-deficient human-induced pluripotent stem cell-derived proliferating myeloid cell lines in cancer therapy.

Hagiwara, S., et al. (2011). "The cancer stem cell marker CD133 is a predictor of the effectiveness of S1+ pegylated interferon alpha-2b therapy against

advanced hepatocellular carcinoma." J Gastroenterol **46**(2): 212-221.

BACKGROUND: Combination therapy with the oral fluoropyrimidine anticancer drug S1 and interferon is reportedly effective for the treatment of advanced hepatocellular carcinoma (HCC), but selection criteria for this therapy have not been clarified. In this study, we attempted to identify factors predicting the effectiveness of this combination therapy. METHODS: Pathological specimens of HCC were collected before treatment from 31 patients with advanced HCC who underwent S1+ pegylated-interferon (PEG-IFN) alpha-2b therapy between January 2007 and January 2009. In these pathological specimens, the expression levels of CD133, thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), and interferon-receptor 2 (IFNR2) proteins were determined by Western blot assay. The presence or absence of p53 gene mutations was determined by direct sequencing. The relationships between these protein expression levels and the response rate (RR), progression-free survival (PFS), and overall survival (OS) were evaluated. RESULTS: The CD133 protein expression level was significantly lower in the responder group than in the nonresponder group. Comparing the PFS and OS between high- and low-level CD133 expression groups (n = 13 and 18, respectively) revealed that both parameters were significantly prolonged in the latter group. The expression levels of TS, DPD, and IFNR2 protein and the presence of p53 gene mutations did not correlate with the RR. CONCLUSIONS: CD133 was identified as a predictor of the therapeutic effect of S1+ PEG-IFN alpha-2b therapy against advanced HCC.

Han, Y. K., et al. (2013). "A possible usage of a CDK4 inhibitor for breast cancer stem cell-targeted therapy." Biochem Biophys Res Commun **430**(4): 1329-1333.

Cancer stem cells (CSCs) are one of the main reasons behind cancer recurrence due to their resistance to conventional anti-cancer therapies. Thus, many efforts are being devoted to developing CSC-targeted therapies to overcome the resistance of CSCs to conventional anti-cancer therapies and decrease cancer recurrence. Differentiation therapy is one potential approach to achieve CSC-targeted therapies. This method involves inducing immature cancer cells with stem cell characteristics into more mature or differentiated cancer cells. In this study, we found that a CDK4 inhibitor sensitized MDA-MB-231 cells but not MCF7 cells to irradiation. This difference appeared to be associated with the relative percentage of CSC-population between the two breast cancer cells. The CDK4 inhibitor induced differentiation and reduced the cancer stem cell activity of MDA-MB-231 cells, which are shown by multiple marker or phenotypes of CSCs. Thus, these results suggest that radiosensitization effects may be caused by reducing the CSC-population of MDA-MB-231 through the use of the CDK4 inhibitor. Thus, further investigations into the possible application of the CDK4 inhibitor for CSC-targeted therapy should be performed to enhance the efficacy of radiotherapy for breast cancer.

Hellman, S., et al. (1983). "Functional organization of the hematopoietic stem cell compartment: implications for cancer and its therapy." J Clin Oncol **1**(4): 277-284.

Recent discoveries indicate that hematopoietic stem cells have limits on their proliferative capacity and are unable to divide indefinitely. There is great heterogeneity within the compartment as to the extent of this proliferative limitation. At any given time it appears that hematopoiesis is maintained by the progeny of only a few stem cells. When these are exhausted the progeny from other stem cells take their place. The observations of proliferative limitation, heterogeneity, and clonal succession must be incorporated into any model of stem cell organization. These new discoveries and the models incorporating them have important clinical implications. They may explain the inability of normal tissues to develop drug resistance and they also offer a mechanism by which cell renewal systems decrease the development of malignancies. In the selection of chemotherapeutic agents not only the effectiveness of the drug upon the tumor must be considered, but also how specific agents affect the stem cell compartment. These data have important implications in the use of bone marrow transplantation for both malignant and nonmalignant disease.

Hendijani, F. and S. H. Javanmard (2015). "Dual Protective and Cytotoxic Benefits of Mesenchymal Stem Cell Therapy in Combination with Chemotherapy/Radiotherapy for Cancer Patients." Crit Rev Eukaryot Gene Expr **25**(3): 203-207.

Cancer is a major health problem in the world, and scientists seek innovative treatment strategies with higher efficacy and lower toxicity than the existing therapeutic agents. In this way, stem cell researchers try to reveal new pathways that will eventually benefit patients. Stem cell research has proven that mesenchymal stem cells (MSCs) possess anticancer activities, and their protein-rich secretome showed similar effects. MSCs also secrete cytokines that play an active role in healing and regeneration processes. Because of their known plasticity, MSCs display a variety of characteristics and functions in different environments, depending on their interactions with

various cell types and tissues. Therefore, we hypothesize that MSC therapy in combination with anticancer medicines can potentiate cytotoxic effects on cancer cells. In addition, because of their regenerative capacity, MSCs can protect normal tissues from adverse cytotoxic drug reactions. They may also help rescue injured tissues from these toxic damages or systemic pathological events that occur during cancer treatment. MSC therapy may double the beneficial effects on cancer and normal cells. As our knowledge of systems biology and biotechnological methodology is progressing, this idea can move forward as a treatment option.

Hennessy, B., et al. (2002). "High dose chemotherapy and stem cell support for poor risk and recurrent nonseminomatous germ cell cancer: initial experience with sequential therapy." Ir J Med Sci **171**(3): 158-160.

BACKGROUND: Approximately 20% of patients with germ cell tumours do not respond fully to standard therapy, or relapse after treatment. The prognosis of these patients is poor with conventional chemotherapy. Preliminary data suggest that they may have a higher durable response rate with high dose chemotherapy and peripheral blood stem cell support. AIMS: To treat a group of testicular cancer patients, either with relapsed disease or with poor prognostic features initially, with high dose chemotherapy and stem cell support, and evaluate their outcome. METHODS: Five patients with testicular cancer were treated with high dose chemotherapy and stem cell support. Of these, four underwent this treatment as salvage therapy and one patient with poor prognostic features was treated as primary treatment. RESULTS: At an average follow-up of 18 months, four patients remain free of disease while one patient has developed relapse. CONCLUSION: This report provides further support for high dose chemotherapy in this setting although randomised, controlled trials are essential to clarify its use.

Herbrecht, R., et al. (2010). "Caspofungin first-line therapy for invasive aspergillosis in allogeneic hematopoietic stem cell transplant patients: an European Organisation for Research and Treatment of Cancer study." Bone Marrow Transplant **45**(7): 1227-1233.

Caspofungin at standard dose was evaluated as first-line monotherapy of mycologically documented probable/proven invasive aspergillosis (IA) (unmodified European Organisation for Research and Treatment of Cancer/Mycosis Study Group criteria) in allogeneic hematopoietic SCT patients. The primary efficacy end point was complete or partial response at end of caspofungin treatment. Response at week 12, survival and safety were additional end points. Enrollment was stopped prematurely because of low accrual, with 42 enrolled and 24 eligible, giving the study a power of 85%. Transplant was from unrelated donors in 16 patients; acute or chronic GVHD was present in 15. In all, 12 patients were neutropenic (<500/microl) at baseline, 10 received steroids and 16 calcineurin inhibitors or sirolimus. Median duration of caspofungin treatment was 24 days. At the end of caspofungin therapy, 10 (42%) patients had complete or partial response (95% confidence interval: 22-63%); 1 (4%) and 12 (50%) had stable and progressing disease, respectively; one was not evaluable. At week 12, eight patients (33%) had complete or partial response. Survival rates at week 6 and 12 were 79 and 50%, respectively. No patient had a drug-related serious adverse event or discontinued because of toxicity. Caspofungin first-line therapy was effective and well tolerated in allogeneic hematopoietic SCT patients with mycologically documented IA.

Hirao, A. (2015). "[Targeted molecular therapy based on advanced cancer stem cell model]." Nihon Rinsho **73**(8): 1256-1262.

Improvement of cell purification and transplantation techniques have contributed to the identification of cell populations known as tumor-initiating cells (TICs). Although it was hypothesized that tumors are organized as hierarchies of tumor cells that are sustained by rare TICs, like normal tissue stem cells, there are several controversies towards such cancer stem cell model, e.g. reversible change of stem cell like population based on epigenetic changes, clonal genetic evolution and problems in xenotransplantation system. Despite complexity in cancer stem cell models, studies in cancer stem cell field have revealed that there are close relationship between cancer malignancy and stem cell properties, called "stemness". Understanding molecular mechanisms for controlling stemness would contribute to establishment of novel diagnostics or therapeutics for cancer.

Hohaus, S., et al. (1999). "Adjuvant high-dose therapy with peripheral blood stem cell support for patients with high-risk breast cancer." Cancer Chemother Pharmacol **44 Suppl**: S13-17.

We report on the efficacy and toxicity of a sequential high-dose therapy with peripheral blood stem cell (PBSC) support in 107 patients with high-risk stage II/III breast cancer. There were 90 patients with more than 9 tumour-positive axillary lymph nodes. An induction therapy of two cycles of ifosfamide (total dose, 7,500 mg/m (2)) and epirubicin (120 mg/m (2)) was given, and PBSC were harvested during granulocyte colony-stimulating factor (G-CSF)-

supported leukocyte recovery following the second cycle. The PBSC-supported high-dose chemotherapy consisted of two cycles of ifosfamide (total dose 12,000 mg/m (2)), carboplatin (900 mg/m (2)) and epirubicin (180 mg/m (2)). Patients were autografted with a median number of 4.1 x 10(6) CD34+ cells/kg (range 1.9-26.5 x 10(6)), resulting in haematological reconstitution within approximately 2 weeks following high-dose therapy. The toxicity was moderate in general, and there was no treatment-related toxic death. Twenty-nine patients (27.1% of all patients) relapsed between 3 and 46 months following the last cycle of high-dose therapy (median 15 months). The probability of disease-free and overall survival at 3 years was 56% and 83%, respectively. A multivariate analysis showed that patients with stage II disease had a significantly better probability of disease-free survival (71%) in comparison with patients with stage III disease (30%). The probability of disease-free survival was also significantly better for patients with oestrogen receptor-positive tumours (62%) compared with patients with receptor-negative ones (40%). In conclusion, sequential high-dose chemotherapy with PBSC support can be safely administered to patients with high-risk stage II/III breast cancer. Further intensification of the therapy including the addition of non-cross-resistant drugs or immunological approaches may be envisaged for patients with stage III disease and hormone receptor-negative tumours.

Hohaus, S., et al. (1998). "Efficacy and toxicity of sequential high-dose therapy with peripheral blood stem cell support in patients with high-risk breast cancer." Semin Oncol **25**(2 Suppl 4): 7-11; discussion 45-18.

Patients with high-risk breast cancer may benefit from dose-escalated chemotherapy. We studied toxicity and therapeutic efficacy of sequential high-dose therapy consisting of two cycles of ifosfamide 12,000 mg/m2, carboplatin 900 mg/m2, and epirubicin 180 mg/m2 (ICE) with peripheral blood stem cell support. Ninety-one patients with advanced breast cancer were included. Fifty-one patients with stage II/III disease and 10 or more tumor-positive axillary lymph nodes received high-dose therapy as adjuvant treatment; the remaining 40 patients were treated for metastatic disease. Peripheral blood stem cells were collected following granulocyte colony-stimulating factor-supported induction chemotherapy. In 68 patients, induction chemotherapy included two cycles of ifosfamide 7,500 mg/m2 and epirubicin 120 mg/m2, while 23 patients received one cycle of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) 135 mg/m2, ifosfamide 6,000 mg/m2, and epirubicin 90 mg/m2. One hundred ninety-two cycles of ICE were supported with a median of 3.5 x 10(6) CD34+ cells/kg body weight (range, 1.7 to 38 x 10(6) CD34+ cells/kg body weight), which resulted in rapid hematologic reconstitution with recovery times, for a median neutrophil count of 0.5 x 10(9)/L of 13 days (range, 6 to 20 days) and for a median platelet count greater than 20 x 10(9)L of 9 days (range, 5 to 24 days). Seven patients received only one cycle of ICE because of progressive disease (in two patients with metastatic disease), central nervous system toxicity (one patient), cardiac toxicity (one patient), severe enterocolitis (one patient), development of human leukocyte antigen antibodies (one patient), and wish to withdraw from the study (one patient). Seventeen patients with metastatic disease received an additional high-dose cycle consisting of the non-cross-resistant agents thiotepa 600 mg/m2, etoposide 1,500 mg/m2, and paclitaxel 165 mg/m2. In patients treated adjuvantly, the probability of disease-free survival was 64% at 47 months, which compares favorably with results of conventional treatment protocols, with a 47% event-free probability at the same time period. The probability of progression-free survival in patients with metastatic disease was 18% at 44 months. In conclusion, sequential high-dose therapy with peripheral blood stem cell support in patients with high-risk breast cancer can be administered safely and offers a potential benefit in the adjuvant setting.

Hsi, E. D., et al. (2008). "Ki67 and PIM1 expression predict outcome in mantle cell lymphoma treated with high dose therapy, stem cell transplantation and rituximab: a Cancer and Leukemia Group B 59909 correlative science study." Leuk Lymphoma **49**(11): 2081-2090.

The proliferation index in mantle cell lymphoma (MCL) has not been validated in the context of aggressive therapy regimens in the rituximab era. We assessed Ki67 and PIM1 (a cell cycle-related gene upregulated in blastoid MCL) expression by immunohistochemistry in a phase II study Cancer and Leukemia Group B 59909 of aggressive chemotherapy and rituximab followed by autologous stem cell transplantation plus rituximab in untreated MCL patients <70 years of age. As a continuous variable or using a cutoff of 35%, higher image analysis (IA Ki67, n = 52) was associated with shorter progression free survival (PFS) (P < or = 0.030) and event free survival (EFS) (P < or = 0.017). PIM1 expression (n = 50) was associated with PFS (P = 0.033) and EFS (P = 0.043). Bivariate Cox models showed IA Ki67 and PIM1 were independent of clinical factors. High Ki67 (>35%) is an important independent prognostic marker in aggressively treated MCL in the rituximab era. PIM1 expression predicts poor outcome and, given its potential role as a therapeutic target, deserves further study.

Hu, W., et al. (2011). "Human umbilical blood mononuclear cell-derived mesenchymal stem cells serve as interleukin-21 gene delivery vehicles for epithelial ovarian cancer therapy in nude mice." Biotechnol Appl Biochem **58**(6): 397-404.

Ovarian cancer causes more deaths than any other cancer of the female reproductive system, and its overall cure rate remains low. The present study investigated human umbilical blood mononuclear cell (UBMC)-derived mesenchymal stem cells (UBMC-MSCs) as interleukin-21 (IL-21) gene delivery vehicles for ovarian cancer therapy in nude mice. MSCs were isolated from UBMCs and the expanded cells were phenotyped by flow cytometry. Cultured UBMCs were differentiated into osteocytes and adipocytes using appropriate media and then the UBMC-MSCs were transfected with recombinant pIRES2-IL-21-enhancement green fluorescent protein. UBMC-MSCs expressing IL-21 were named as UBMC-MSC-IL-21. Mice with A2780 ovarian cancer were treated with UBMC-MSC-IL-21 intravenously, and the therapeutic efficacy was evaluated by the tumor volume and mouse survival. To address the mechanism of UBMC-MSC-IL-21 against ovarian cancer, the expression of IL-21, natural killer glucoprotein 2 domain and major histocompatibility complex class I chain-related molecules A/B were detected in UBMC-MSC-IL-21 and in the tumor sites. Interferon-gamma-secreting splenocyte numbers and natural killer cytotoxicity were significantly increased in the UBMC-MSC-IL-21-treated mice as compared with the UBMC-MSCs or the UBMC-MSC-mock plasmid-treated mice. Most notably, tumor growth was delayed and survival was prolonged in ovarian-cancer-bearing mice treated with UBMC-MSC-IL-21. Our data provide important evidence that UBMC-MSCs can serve as vehicles for IL-21 gene delivery and inhibit the established tumor.

Imataki, O., et al. (2006). "Intensive multimodality therapy including paclitaxel and reduced-intensity allogeneic hematopoietic stem cell transplantation in the treatment of adrenal cancer with multiple metastases." Int J Clin Oncol **11**(2): 156-158.

Adrenocortical carcinoma is a rare malignancy in adolescents and young adults. The prognosis of unresectable/metastatic adrenocortical carcinoma remains very poor because the rarity of the tumor has made it difficult to establish treatment guidelines, and diagnosis and the resultant treatment can be greatly delayed. We treated a 24-year-old woman who was diagnosed with adrenocortical carcinoma of the right adrenal gland which extended to the inferior vena cava. Although she underwent surgical resection of the extensive tumor as the primary treatment, the disease recurred in the lung and liver as multiple metastases shortly after surgery. She received intensive multimodality therapy, including chemotherapy with paclitaxel, ifosfamide, and cisplatin (TIP regimen), embolization of the feeding arteries, and proton irradiation for the liver mass. Finally, she underwent reduced-intensity allogeneic hematopoietic stem cell transplantation from an HLA 1-locus-mismatched sibling donor. A prolonged survival of 39 months after the onset of the disease was achieved. Although this experience is limited, we suggest that TIP chemotherapy was effective for adrenocortical carcinoma, and a graft-versus-tumor effect after reduced-intensity stem cell transplantation may have contributed to the prolonged survival.

Iwamoto, H., et al. (2013). "[Cancer vaccine therapy using genetically modified induced pluripotent stem cell-derived dendritic cells expressing the TAA gene]." Gan To Kagaku Ryoho **40**(12): 1575-1577.

It is generally accepted that the difficulty in obtaining a sufficient number of functional dendritic cells (DCs) poses a serious problem in DC-based immunotherapy. Therefore, we used induced pluripotent stem (iPS) cell-derived DCs (iPSDCs) instead. If the therapeutic efficacy of iPSDCs was equivalent to that of bone marrow-derived DCs (BMDCs), then the above-mentioned problems may be solved. In this study, we generated iPSDCs from iPS cells and compared their capacity to mature and migrate to the regional lymph nodes with that of BMDCs. We adenovirally transduced the hgp100 gene, which codes for a natural tumor antigen, into the DCs and immunized the mice with these genetically modified DCs. The cytotoxic activity of CD8(+) cytotoxic T lymphocytes (CTLs) was assayed using a 51Cr-release assay. The therapeutic efficacy of the vaccination was examined in a subcutaneous tumor model. Our results demonstrated that iPSDCs equaled BMDCs in terms of their maturation and migration capacity. Furthermore, hgp100-specific CTLs were generated in mice that were immunized with the genetically modified iPSDCs. These CTLs exhibited a high level of cytotoxicity against B16 cells, which is similar to that exhibited by CTLs generated in BMDCs immunized mice. Moreover, vaccination with genetically modified iPSDCs elicited a high level of therapeutic efficacy equaling that of vaccination with BMDCs. This study clarified experimentally that genetically modified iPSDCs are equivalent to BMDCs in terms of tumor-associated antigen-specific therapeutic antitumor immunity. This vaccination strategy may therefore be useful for future clinical application as a cancer vaccine.

Jacobs, S. R., et al. (2007). "Evaluation of the functional assessment of cancer therapy cognitive scale with hematopoietic stem cell transplant patients." J Pain Symptom Manage **33**(1): 13-23.

The current study evaluated a newly developed self-report measure of cognitive complaints with cancer patients, the Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog). Six or 12 months following hematopoietic stem cell transplantation, participants completed a psychosocial assessment that included the FACT-Cog and a neuropsychological assessment. Using a criterion of two or more times a week, an average of 12 of a total of 50 items were endorsed as complaints on the FACT-Cog. FACT-Cog total, domain, and subscale scores were significantly correlated with measures of depression, fatigue, anxiety, and physical and mental well-being. FACT-Cog scores, with the exception of one subscale, Other People Noticed Deficits, were not significantly correlated with cognitive performance. In general, the FACT-Cog and a commonly used measure of cognitive complaints (European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 Cognitive Functioning Scale) demonstrated similar psychometric properties. However, the FACT-Cog assesses broader aspects of cognitive complaints, thereby providing greater information about the types of cognitive complaints patients are experiencing.

Jang, E., et al. (2016). "Nanovesicle-mediated systemic delivery of microRNA-34a for CD44 overexpressing gastric cancer stem cell therapy." Biomaterials **105**: 12-24.

The cancer stem cell (CSC) hypothesis postulates that cancer cells overexpressing CD44 are marked as CSCs that cause tumorigenesis and recurrence. This hypothesis suggests that CD44 is a potential therapeutic target that can interfere with CSCs qualities. MicroRNA-34a (miR-34a) is a promising candidate for CD44 repression-based cancer therapy as it has been reported to inhibit proliferation, metastasis, and survival of CD44-positive CSCs. Here, we used nanovesicles containing PLI/miR complexes (NVs/miR) to systemically deliver miR-34a and induce miR-34a-triggered CD44 suppression in orthotopically and subcutaneously implanted tumors in nude mice. Poly (l-lysine-graft-imidazole) (PLI) condenses miRs and is functionally modified to deliver miRs to the site of action by buffering effect of imidazole residues under endosomal pH. Indeed, NVs/miR consisting of PEGylated lipids enveloping PLI/miR complexes greatly reduced inevitable toxicity of polycations by compensating their surface charge and markedly improved their in vivo stability and accumulation to tumor tissue compared to PLI/miR polyplexes. Our NVs-mediated miR-34a delivery system specifically increased endogenous target miR levels, thereby attenuating proliferation and migration of gastric cancer cells by repressing the expression of CD44 with decreased levels of Bcl-2, Oct 3/4 and Nanog genes. Our strategy led to a greater therapeutic outcome than PLI-based delivery with highly selective tumor cell death and significantly delayed tumor growth in CD44-positive tumor-bearing mouse models, thus providing a fundamental therapeutic window for CSCs.

Jenq, R. R. and M. R. van den Brink (2010). "Allogeneic haematopoietic stem cell transplantation: individualized stem cell and immune therapy of cancer." Nat Rev Cancer **10**(3): 213-221.

The year 2009 marked the fiftieth anniversary of the first successful allogeneic haematopoietic stem cell transplant (HSCT). The field of HSCT has pioneered some of the most exciting areas of research today. HSCT was the original stem cell therapy, the first cancer immune therapy and the earliest example of individualized cancer therapy. In this Timeline article we review the history of the development of HSCT and major advances made in the past 50 years. We highlight accomplishments made by researchers who continue to strive to improve outcomes for patients and increase the availability of this potentially life-saving therapy for patients with otherwise incurable malignancies.

Kakarala, M. and M. S. Wicha (2008). "Implications of the cancer stem-cell hypothesis for breast cancer prevention and therapy." J Clin Oncol **26**(17): 2813-2820.

Recent research in breast biology has provided support for the cancer stem-cell hypothesis. Two important components of this hypothesis are that tumors originate in mammary stem or progenitor cells as a result of dysregulation of the normally tightly regulated process of self-renewal. As a result, tumors contain and are driven by a cellular subcomponent that retains key stem-cell properties including self-renewal, which drives tumorigenesis and differentiation that contributes to cellular heterogeneity. Advances in stem-cell technology have led to the identification of stem cells in normal and malignant breast tissue. The study of these stem cells has helped to elucidate the origin of the molecular complexity of human breast cancer. The cancer stem-cell hypothesis has important implications for early detection, prevention, and treatment of breast cancer. Both hereditary and sporadic breast cancers may develop through dysregulation of stem-cell self-renewal pathways. These aberrant stem cells may provide targets for the development of cancer prevention strategies.

Furthermore, because breast cancer stem cells may be highly resistant to radiation and chemotherapy, the development of more effective therapies for this disease may require the effective targeting of this cell population.

Kannan, N., et al. (2014). "Integrin beta3 links therapy resistance and cancer stem cell properties." Nat Cell Biol **16**(5): 397-399.

Heterogeneity in tumour cell properties underlies many treatment failures. Understanding the sources of such heterogeneity has proved to be challenging, but remains critical to improving patient outcomes. Integrin alpha (v)beta (3) expression in multiple types of solid tumour stem cells is now shown to control a pro-survival pathway that contributes to therapy resistance.

Keraliya, A. R., et al. (2015). "Imaging of Fluid in Cancer Patients Treated With Systemic Therapy: Chemotherapy, Molecular Targeted Therapy, and Hematopoietic Stem Cell Transplantation." AJR Am J Roentgenol **205**(4): 709-719.

OBJECTIVE: The purpose of this article is to provide a comprehensive review of the imaging features of various systemic treatment-related causes of fluid accumulation in cancer patients. CONCLUSION: Systemic treatment-related fluid accumulation can occur with chemotherapy, molecular targeted therapy, or hematopoietic stem cell transplantation. Imaging findings such as new ascites, pleural and pericardial effusions, and subcutaneous edema should be interpreted with caution on restaging studies.

Kerk, S. A., et al. (2017). "5T4-Targeted Therapy Ablates Cancer Stem Cells and Prevents Recurrence of Head and Neck Squamous Cell Carcinoma." Clin Cancer Res **23**(10): 2516-2527.

Purpose: Locoregional recurrence is a frequent treatment outcome for patients with advanced head and neck squamous cell carcinoma (HNSCC). Emerging evidence suggests that tumor recurrence is mediated by a small subpopulation of uniquely tumorigenic cells, that is, cancer stem cells (CSC), that are resistant to conventional chemotherapy, endowed with self-renewal and multipotency.Experimental Design: Here, we evaluated the efficacy of MEDI0641, a novel antibody-drug conjugate targeted to 5T4 and carrying a DNA-damaging "payload" (pyrrolobenzodiazepine) in preclinical models of HNSCC.Results: Analysis of a tissue microarray containing 77 HNSCC with follow-up of up to 12 years revealed that patients with 5T4(high) tumors displayed lower overall survival than those with 5T4(low) tumors (P = 0.038). 5T4 is more highly expressed in head and neck CSC (ALDH (high)CD44(high)) than in control cells (non-CSC). Treatment with MEDI0641 caused a significant reduction in the CSC fraction in HNSCC cells (UM-SCC-11B, UM-SCC-22B) in vitro Notably, a single intravenous dose of 1 mg/kg MEDI0641 caused long-lasting tumor regression in three patient-derived xenograft (PDX) models of HNSCC. MEDI0641 ablated CSC in the PDX-SCC-M0 model, reduced it by five-fold in the PDX-SCC-M1, and two-fold in the PDX-SCC-M11 model. Importantly, mice (n = 12) treated with neoadjuvant, single administration of MEDI0641 prior to surgical tumor removal showed no recurrence for more than 200 days, whereas the control group had 7 recurrences (in 12 mice; P = 0.0047).Conclusions: Collectively, these findings demonstrate that an anti-5T4 antibody-drug conjugate reduces the fraction of CSCs and prevents local recurrence and suggest a novel therapeutic approach for patients with HNSCC. Clin Cancer Res; 23(10); 2516-27. (c)2016 AACR.

Kim, H., et al. (2015). "Successful empirical antifungal therapy of intravenous itraconazole with pharmacokinetic evidence in pediatric cancer patients undergoing hematopoietic stem cell transplantation." Clin Drug Investig **35**(7): 437-446.

BACKGROUND AND OBJECTIVES: Empirical antifungal therapy prevents invasive fungal infections in patients with cancer. This study assessed the empirical efficacy of intravenous itraconazole in pediatric patients undergoing hematopoietic stem cell transplantation, and investigated the pharmacokinetics and clinical implications. METHODS: Oral itraconazole syrup was started (2.5 mg/kg twice daily) for prophylaxis, and patients with persistent neutropenic fever for more than 2 days were switched to intravenous itraconazole (5 mg/kg twice daily for 2 days for induction and 5 mg/kg daily for maintenance) as empirical treatment. Empirical antifungal efficacy was assessed retrospectively in 159 transplantations, and a full pharmacokinetic study was prospectively conducted in six of these patients. Successful antifungal efficacy was defined as the fulfillment of all components of a five-part composite end point. RESULTS: The overall empirical antifungal success rate fulfilling all criteria was 42.1 %. No death or drug-related serious adverse events occurred during the study. Mean trough plasma concentration of itraconazole after oral prophylaxis and intravenous induction were 577.2 and 1659.7 mug/L, respectively. Mean area under the concentration-time curve of itraconazole and its metabolite at steady state were 42,837 +/- 24,746 mug.h/L and 63,094 +/- 19,255 mug.h/L. CONCLUSIONS: Intravenous itraconazole was effective and safe as an empirical antifungal agent

in pediatric patients; this was due to the fast and satisfactory increase in drug concentration by switching from oral to intravenous therapy.

Kim, J. H., et al. (2014). "Stem cell based gene therapy in prostate cancer." Biomed Res Int **2014**: 549136.

Current prostate cancer treatment, especially hormone refractory cancer, may create profound iatrogenic outcomes because of the adverse effects of cytotoxic agents. Suicide gene therapy has been investigated for the substitute modality for current chemotherapy because it enables the treatment targeting the cancer cells. However the classic suicide gene therapy has several profound side effects, including immune-compromised due to viral vector. Recently, stem cells have been regarded as a new upgraded cellular vehicle or vector because of its homing effects. Suicide gene therapy using genetically engineered mesenchymal stem cells or neural stem cells has the advantage of being safe, because prodrug administration not only eliminates tumor cells but consequently kills the more resistant therapeutic stem cells as well. The attractiveness of prodrug cancer gene therapy by stem cells targeted to tumors lies in activating the prodrug directly within the tumor mass, thus avoiding systemic toxicity. Therapeutic achievements using stem cells in prostate cancer include the cytosine deaminase/5-fluorocytosine prodrug system, herpes simplex virus thymidine kinase/ganciclovir, carboxyl esterase/CPT11, and interferon-beta. The aim of this study is to review the stem cell therapy in prostate cancer including its proven mechanisms and also limitations.

Kim, S. H., et al. (2016). "Prostate Stem Cell Antigen Expression in Radical Prostatectomy Specimens Predicts Early Biochemical Recurrence in Patients with High Risk Prostate Cancer Receiving Neoadjuvant Hormonal Therapy." PLoS One **11**(3): e0151646.

We aimed to identify tissue biomarkers that predict early biochemical recurrence (BCR) in patients with high-risk prostate cancer (PC), toward the goal of increasing the benefits of neoadjuvant hormonal therapy (NHT). In 2005-2012, prostatectomy specimens were collected from 134 PC patients who had received NHT and radical prostatectomy. The expression of 13 tissue biomarkers was assessed in the specimens via immunohistochemistry. Time to BCR and factors predictive of BCR were determined by using the Cox proportional hazards model. During the follow-up period (median, 57.5 months), 67 (50.0%) patients experienced BCR. Four (3.0%) patients were tumor-free in the final pathology assessment, and 101 (75.4%) had negative resection margins. Prostate stem cell antigen (PSCA) was the only significant prognostic tissue biomarker of BCR [hazard ratio (HR), 2.58; 95% confidence interval (CI), 1.06-6.27; p = 0.037] in a multivariable analysis adjusted by the clinicopathological variables that also significantly predicted BCR; these were seminal vesicle invasion (HR, 2.39; 95% CI, 1.32-4.34), initial prostate serum antigen level (HR 1.01; 95% CI, 1.001-1.020), prostate size (HR, 0.93; 95% CI, 0.90-0.97), and the Gleason score of preoperative biopsies (HR, 1.34; 95% CI, 1.01-1.79). We suggest that PSCA is a useful tissue marker for predicting BCR in patients with high risk PC receiving NHT and radical prostatectomy.

Kitamura, H., et al. (2009). "Cancer stem cell: implications in cancer biology and therapy with special reference to lung cancer." Lung Cancer **66**(3): 275-281.

The cancer stem cell (CSC) theory is currently central to the field of cancer research, because it is not only a matter of academic interest but also crucial in cancer therapy. CSCs share a variety of biological properties with normal somatic stem cells in terms of self-renewal, the propagation of differentiated progeny, the expression of specific cell markers and stem cell genes, and the utilization of common signaling pathways and the stem cell niche. However, CSCs differ from normal stem cells in their tumorigenic activity. Thus, CSCs are also termed cancer initiating cells. In this paper, we briefly review hitherto described study results and refer to some excellent review articles to understand the basic properties of CSCs. In addition, we focus upon CSCs of lung cancers, since lung cancer is still increasing in incidence worldwide and remains the leading cause of cancer deaths. Understanding the properties of, and exploring cell markers and signaling pathways specific to, CSCs of lung cancers, will lead to progress in therapy, intervention, and improvement of the prognosis of patients with lung cancer. In the near future, the evaluation of CSCs may be a routine part of practical diagnostic pathology.

Knoop, K., et al. (2011). "Image-guided, tumor stroma-targeted 131I therapy of hepatocellular cancer after systemic mesenchymal stem cell-mediated NIS gene delivery." Mol Ther **19**(9): 1704-1713.

Due to its dual role as reporter and therapy gene, the sodium iodide symporter (NIS) allows noninvasive imaging of functional NIS expression by (123)I-scintigraphy or (124)I-PET imaging before the application of a therapeutic dose of (131)I. NIS expression provides a novel mechanism for the evaluation of mesenchymal stem cells (MSCs) as gene delivery vehicles for tumor therapy. In the current study, we stably transfected bone marrow-derived

CD34(-) MSCs with NIS cDNA (NIS-MSC), which revealed high levels of functional NIS protein expression. In mixed populations of NIS-MSCs and hepatocellular cancer (HCC) cells, clonogenic assays showed a 55% reduction of HCC cell survival after (131)I application. We then investigated body distribution of NIS-MSCs by (123)I-scintigraphy and (124)I-PET imaging following intravenous (i.v.) injection of NIS-MSCs in a HCC xenograft mouse model demonstrating active MSC recruitment into the tumor stroma which was confirmed by immunohistochemistry and ex vivo gamma-counter analysis. Three cycles of systemic MSC-mediated NIS gene delivery followed by (131)I application resulted in a significant delay in tumor growth. Our results demonstrate tumor-specific accumulation and therapeutic efficacy of radioiodine after MSC-mediated NIS gene delivery in HCC tumors, opening the prospect of NIS-mediated radionuclide therapy of metastatic cancer using MSCs as gene delivery vehicles.

Knoop, K., et al. (2015). "Mesenchymal stem cell-mediated, tumor stroma-targeted radioiodine therapy of metastatic colon cancer using the sodium iodide symporter as theranostic gene." J Nucl Med **56**(4): 600-606.

UNLABELLED: The tumor-homing property of mesenchymal stem cells (MSCs) allows targeted delivery of therapeutic genes into the tumor microenvironment. The application of sodium iodide symporter (NIS) as a theranostic gene allows noninvasive imaging of MSC biodistribution and transgene expression before therapeutic radioiodine application. We have previously shown that linking therapeutic transgene expression to induction of the chemokine CCL5/RANTES allows a more focused expression within primary tumors, as the adoptively transferred MSC develop carcinoma-associated fibroblast-like characteristics. Although RANTES/CCL5-NIS targeting has shown efficacy in the treatment of primary tumors, it was not clear if it would also be effective in controlling the growth of metastatic disease. METHODS: To expand the potential range of tumor targets, we investigated the biodistribution and tumor recruitment of MSCs transfected with NIS under control of the RANTES/CCL5 promoter (RANTES-NIS-MSC) in a colon cancer liver metastasis mouse model established by intrasplenic injection of the human colon cancer cell line LS174t. RANTES-NIS-MSCs were injected intravenously, followed by (123)I scintigraphy, (124)I PET imaging, and (131)I therapy. RESULTS: Results show robust MSC recruitment with RANTES/CCL5-promoter activation within the stroma of liver metastases as evidenced by tumor-selective iodide accumulation, immunohistochemistry, and real-time polymerase chain reaction. Therapeutic application of (131)I in RANTES-NIS-MSC-treated mice resulted in a significant delay in tumor growth and improved overall survival. CONCLUSION: This novel gene therapy approach opens the prospect of NIS-mediated radionuclide therapy of metastatic cancer after MSC-mediated gene delivery.

Knorr, D. A. and D. S. Kaufman (2010). "Pluripotent stem cell-derived natural killer cells for cancer therapy." Transl Res **156**(3): 147-154.

Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) provide an accessible, genetically tractable, and homogenous starting cell population to efficiently study human blood cell development. These cell populations provide platforms to develop new cell-based therapies to treat both malignant and nonmalignant hematological diseases. Our group previously demonstrated the ability of hESC-derived hematopoietic precursors to produce functional natural killer (NK) cells as well as an explanation of the underlying mechanism responsible for the inefficient development of T and B cells from hESCs. hESCs and iPSCs, which can be engineered reliably in vitro, provide an important new model system to study human lymphocyte development and produce enhanced cell-based therapies with the potential to serve as a "universal" source of antitumor lymphocytes. This review will focus on the application of hESC-derived NK cells with currently used and novel therapeutics for clinical trials, barriers to translation, and future applications through genetic engineering approaches.

Kolstad, A., et al. (1996). "[High-dose therapy with autologous stem cell support in malignant lymphoma and breast cancer. Experiences with hematopoietic stem cells isolate from blood]." Tidsskr Nor Laegeforen **116**(21): 2547-2551.

Since 1994, 17 breast cancer patients and 16 lymphoma patients have been treated at the Norwegian Radium Hospital with high-dose therapy supported by autologous peripheral progenitor cells. All the patients were given granulocyte colony stimulating factor in the recovery phase after cytotoxic treatment in order to mobilize and harvest peripheral progenitor cells. Aphareses were successful in all patients and the mean number of CD34 cells reinfused per kilo body weight was 7.05 x 10(6) for the lymphoma patients and 11.1 x 10(6) for the breast cancer patients. The mean time to recover > or = 0.5 x 10(9)/l granulocytes and > or = 20 x 10(9)/l platelets after reinfusion of stem cells was 10 days and 11.7 days respectively for the lymphoma patients, while the breast cancer patients engrafted at

day 8.6 and day 9.3. No severe treatment-related complications were observed.

Korbling, M. (1995). "Blood stem cell transplantation and gene therapy of cancer." Stem Cells **13 Suppl 3**: 106-113.

Based on the concept of circulating hematopoietic stem cells with indefinite self-renewal capacity that gives rise to all three cell lineages, peripheral blood progenitor cells (PBPCs) have widely replaced the use of bone marrow (BM) progenitors for autologous transplantation purposes in patients with malignant hematological disorders and selected solid tumors. Ex vivo purification of normal CD34+ cell subsets contained in the patient's apheresis product possibly eliminates clonogenic tumor cells, but also serves as a target cell population for gene transduction. Genetic tagging of PBPC autografts has proven that: 1) NEOR gene expression is sustained for more than 18 months and 2) clonogenic tumor cells contaminating the autograft contribute to relapse. A second generation of gene transduction studies includes new treatment strategies such as the induction of chemoprotection (multidrug resistance gene-1), chemotherapy sensitization (p53), cancer vaccination and genetic chemosensitization. Most recently allogeneic PBPC transplantation has successfully been introduced with the intention of improving the graft-versus-leukemia effect without inducing a higher incidence or more severe graft-versus-host disease (GVHD) than what is expected after BM transplantation. Introducing the herpes virus thymidine kinase cDNA into activated donor T cells makes them susceptible to gangciclovir, thus allowing the in vivo inactivation of GVHD-inducing T cells. With the close interaction of molecular genetics and clinical oncology/hematology, genetic engineering of stem cell grafts will lead into a new stage of stem cell transplantation technology.

Kotasek, D., et al. (1994). "Dose intensive therapy with autologous blood stem cell transplantation in breast cancer." Aust N Z J Med **24**(3): 288-295.

BACKGROUND: Breast cancer is the commonest form of cancer in Australian women. Although approximately 50% of women with breast cancer achieve long term survival by current management methods, recurrent or metastatic disease is generally incurable. In addition, women with Stage II disease with > 10 positive axillary lymph nodes and also women with locally advanced disease (Stage III) have a poor survival even with adjuvant therapy. AIMS: To assess the toxicity and efficacy of high-dose chemotherapy with autologous peripheral blood stem cell (PBSC) transplantation in women with both metastatic and poor prognosis primary breast cancer. METHODS: Twenty-eight women with either metastatic (15) or poor prognosis (13) primary breast cancer were enrolled in the study between November 1988 to January 1993. PBSC were harvested using high-dose cyclophosphamide (Cy) with or without granulocyte-colony stimulating factor (G-CSF) and a myeloablative regimen of Cy, melphalan and carboplatin (CMCp) was used in the transplantation phase. RESULTS: Optimum numbers of stem cells were harvested in 85% of patients. The use of five G/m2 Cy plus G-CSF resulted in better PBSC yields and a significant reduction in haematologic morbidity when compared to mobilisation with Cy alone. Twenty-two women underwent 23 PBSC transplants (PBSCT). There have been two early deaths due to sepsis. The predominant morbidities observed following high dose chemotherapy and transplantation have been nausea, mucositis and diarrhoea. The median number of days to discharge following infusion of PBSC was 15 (range 11-21). At a median follow up time of 1.1 years (range 0 months-3.6 years), 8/22 (36%) evaluable patients remain alive and disease free while 14/22 (64%) have relapsed or progressed or died. CONCLUSION: High-dose chemotherapy and autologous PBSCT is a potentially highly effective treatment of women with metastatic and poor prognosis primary breast cancer. Randomised studies are required to compare this form of therapy to more standard forms of treatment in breast cancer.

Kvalheim, G., et al. (1996). "[High-dose therapy of cancer with CD34 positive cells as stem cell support]." Tidsskr Nor Laegeforen **116**(21): 2542-2546.

In this article we report our initial clinical experiences in connection with immunomagnetic isolated CD34-positive cells from peripheral blood progenitor cells. Six patients, five with breast cancer and one with non-Hodgkin's lymphoma, were mobilized by chemotherapy and G-CSF (5ug/kg). CD34-positive cells were isolated by means of immunomagnetic beads (Dynalbeads) and Isolex 300 Cell Separator (Baxter, USA). Mean purity of isolated CD34-positive cells was 97% (94.7-99.7) and mean yield was 54% (35-68). Three patients were treated with high dose therapy followed by reinfusion of CD34-positive cells as stem cell support. Recovery of neutrophils (> 0.5 x 10(9) leucocytes/liter) occurred at day 8, 11 and 13 and of platelets (> 20 x 10(9) platelets/litre) at day 9,14 and 32. It is concluded that immunomagnetic isolated CD34-positive cells give high purity and yield. Although use of CD34-positive cells reduces the content of contaminating tumour cells in the graft, breast cancer cells were still detectable in two out of five CD34-positive cell products.

Leal, J. A., et al. (2013). "Stem cell microRNAs in senescence and immortalization: novel players in cancer therapy." Med Res Rev **33**(1): 112-138.

The molecular etiology of malignancy remains one of the most challenging disease processes under scientific investigation; therefore, improved approaches for their treatment are urgently needed. MicroRNAs are highly conserved nonprotein-coding RNAs that regulate gene expression. They are involved in important homeostatic processes, such as cellular proliferation, cell death and development, and affect many diseases, including cancer. High-throughput screenings based on microRNAs related to senescence/immortalization are potential tools for identifying novel proliferative microRNAs that might be involved in carcinogenesis. Recently, a subgroup of highly proliferative microRNAs, which belong to a cluster expressed exclusively in embryonic stem cells and their malignant derivatives (embryonic carcinoma cells), was revealed to play a role in senescence bypass, thereby providing immortalization to human cells. This finding supports the cancer stem cell theory and the relevance of microRNAs in human tumors. This article recapitulates the role of microRNAs that are associated with stem cell properties and their possible link in common pathways related to immortalization and cancer. Ultimately, cancer therapy that is based on the induction of a senescence response is proposed to be highly associated with the loss of stemness properties. Thus, it would be possible to "kill two birds with one stone": along with the inhibition of stemness properties in cancer stem cells, the senescence response could be induced to destroy the cancer stem cell population within a tumor.

Lee, H. E., et al. (2011). "An increase in cancer stem cell population after primary systemic therapy is a poor prognostic factor in breast cancer." Br J Cancer **104**(11): 1730-1738.

BACKGROUND: The cancer stem cell (CSC) hypothesis has important clinical implications for cancer therapeutics because of the proposed role of CSCs in chemoresistance. The aim of this study was to investigate changes in the CSC populations before and after primary systemic therapy (PST) and their prognostic role in human breast cancer. METHODS: Paired samples (before and after PST) of breast cancer tissue were obtained from clinical stage II or III patients (n=92) undergoing PST with the regimen of doxorubicin plus docetaxel (AD) (n=50) or doxorubicin plus cyclophosphamide (AC) (n=42) and subsequent breast resection. The proportions of putative CSCs with CD44+/CD24- or aldehyde dehydrogenase 1+ (ALDH1+) phenotypes were determined by immunohistochemistry. RESULTS: A higher proportion of CD44+/CD24- tumour cells and ALDH1 positivity in pre-chemotherapy tissue was correlated with higher histologic grade, oestrogen receptor (ER) negativity, high Ki-67 proliferation index and basal-like subtype of breast cancer. Aldehyde dehydrogenase 1 positivity in pre-chemotherapy biopsy was also associated with a higher rate of pathologic complete response following PST. In comparisons of putative CSC populations before and after PST, the proportions of CD44+/CD24- and ALDH1+ tumour cells were significantly increased after PST. The cases with increased CD44+/CD24- tumour cell populations after PST showed high Ki-67 proliferation index in post-chemotherapy specimens and those with increased ALDH1+ tumour cell population after PST were associated with ER negativity and p53 overexpression. Furthermore, cases showing such an increase had significantly shorter disease-free survival time than those with no change or a reduced number of CSCs, and the survival difference was most notable with regard to the changes of ALDH1+ tumour cell population in the patients who received AC regimen. CONCLUSION: The present study provides the clinical evidence that the putative CSCs in breast cancer are chemoresistant and are associated with tumour progression, emphasising the need for targeting of CSCs in the breast cancer therapeutics.

Lenos, K. J., et al. (2018). "Stem cell functionality is microenvironmentally defined during tumour expansion and therapy response in colon cancer." Nat Cell Biol **20**(10): 1193-1202.

Solid malignancies have been speculated to depend on cancer stem cells (CSCs) for expansion and relapse after therapy. Here we report on quantitative analyses of lineage tracing data from primary colon cancer xenograft tissue to assess CSC functionality in a human solid malignancy. The temporally obtained clone size distribution data support a model in which stem cell function in established cancers is not intrinsically, but is entirely spatiotemporally orchestrated. Functional stem cells that drive tumour expansion predominantly reside at the tumour edge, close to cancer-associated fibroblasts. Hence, stem cell properties change in time depending on the cell location. Furthermore, although chemotherapy enriches for cells with a CSC phenotype, in this context functional stem cell properties are also fully defined by the microenvironment. To conclude, we identified osteopontin as a key cancer-associated fibroblast-produced factor that drives in situ clonogenicity in colon cancer.

Leung, E. Y., et al. (2017). "Endocrine Therapy of Estrogen Receptor-Positive Breast Cancer Cells:

Early Differential Effects on Stem Cell Markers." Front Oncol **7**: 184.

INTRODUCTION: Endocrine therapy of breast cancer, which either deprives cancer tissue of estrogen or prevents estrogen pathway signaling, is the most common treatment after surgery and radiotherapy. We have previously shown for the estrogen-responsive MCF-7 cell line that exposure to tamoxifen, or deprivation of estrogen, leads initially to inhibition of cell proliferation, followed after several months by the emergence of resistant sub-lines that are phenotypically different from the parental line. We examined the early responses of MCF-7 cells following either exposure to 4-hydroxytamoxifen or deprivation of estrogen for periods of 2 days-4 weeks. METHODS: Endocrine-sensitive or -resistant breast cancer cell lines were used to examine the expression of the stem cell gene SOX2, and the Wnt effector genes AXIN2 and DKK1 using quantitative PCR analysis. Breast cancer cell lines were used to assess the anti-proliferative effects (as determined by IC50 values) of Wnt pathway inhibitors LGK974 and IWP-2. RESULTS: Hormone therapy led to time-dependent increases of up to 10-fold in SOX2 expression, up to threefold in expression of the Wnt target genes AXIN2 and DKK1, and variable changes in NANOG and OCT4 expression. The cells also showed increased mammosphere formation and increased CD24 surface protein expression. Some but not all hormone-resistant MCF-7 sub-lines, emerging after long-term hormonal stress, showed up to 50-fold increases in SOX2 expression and smaller increases in AXIN2 and DKK1 expression. However, the increase in Wnt target gene expression was not accompanied by an increase in sensitivity to Wnt pathway inhibitors LGK974 and IWP-2. A general trend of lower IC50 values was observed in 3-dimensional spheroid culture conditions (which allowed enrichment of cells with cancer stem cell phenotype) relative to monolayer cultures. The endocrine-resistant cell lines showed no significant increase in sensitivity to Wnt inhibitors. CONCLUSION: Hormone treatment of cultured MCF-7 cells leads within 2 days to increased expression of components of the SOX2 and Wnt pathways and to increased potential for mammosphere formation. We suggest that these responses are indicative of early adaptation to endocrine stress with features of stem cell character and that this facilitates the survival of emerging hormone-resistant cell populations.

Li, K., et al. (2009). "[Cancer stem cell theory and cancer therapy]." Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi **23**(1): 30-33.

OBJECTIVE: To analyze the advances of cancer stem cell (CSC) in recent years, and to propose a prospect for CSC research and cancer therapy. METHODS: Articles about important advances of CSC theory and cancer therapy were reviewed, and then selected and summarized. RESULTS: In 2001, CSC was first put forward as a concept, till now, which has been confirmed in many tissues. In recent years, efforts were dedicated to such topics including: identification of CSC in solid tumors, the origin of CSC, its niche and growth mechanism, cancer therapy, etc. According to the CSC theory, traditional therapeutic methods have deficiencies, and new treatment targeting CSC may thoroughly eliminate tumors. CONCLUSION: At present, CSC theory is still controversial, while it proposed revolutionary methods and directions for the therapy of cancer.

Li, Z., et al. (2009). "Toward a stem cell gene therapy for breast cancer." Blood **113**(22): 5423-5433.

Current approaches for treatment of late-stage breast cancer rarely result in a long-term cure. In part this is due to tumor stroma that prevents access of systemically or intratumorally applied therapeutics. We propose a stem cell gene therapy approach for controlled tumor stroma degradation that uses the pathophysiologic process of recruitment of inflammatory cells into the tumor. This approach involves genetic modification of hematopoietic stem cells (HSCs) and their subsequent transplantation into tumor-bearing mice. We show that inducible, intratumoral expression of relaxin (Rlx) either by transplanting tumor cells that contained the Rlx gene or by transplantation of mouse HSCs transduced with an Rlx-expressing lentivirus vector delays tumor growth in a mouse model of breast cancer. The antitumor effect of Rlx was mediated through degradation of tumor stroma, which provided increased access of infiltrating antitumor immune cells to their target tumor cells. Furthermore, we have shown in a human/mouse chimeric model that genetically modified HSCs expressing a transgene can access the tumor site. Our findings are relevant for cancer gene therapy and immunotherapy.

Liu, D. Q. and X. T. Pei (2005). "[Hope to the cancer therapy: cancer stem cell]." Zhongguo Yi Xue Ke Xue Yuan Xue Bao **27**(6): 659-661.

Cancer stem cells are defined as rare cells in cancer tissues with indefinite potential for self-renewal that drives tumorigenesis. It was first extensively documented for leukaemia and multiple myeloma. It has also been found in solid cancers such as human breast cancer and nervous system tumors. Studies of cancer stem cell biology and mechanisms of tumorigenesis are lending insight into the origins of cancer and will ultimately yield new approaches to fight cancer.

Liu, X., et al. (2013). "Nonlinear growth kinetics of breast cancer stem cells: implications for cancer stem cell targeted therapy." Sci Rep **3**: 2473.

Cancer stem cells (CSCs) have been identified in primary breast cancer tissues and cell lines. The CSC population varies widely among cancerous tissues and cell lines, and is often associated with aggressive breast cancers. Despite of intensive research, how the CSC population is regulated within a tumor is still not well understood so far. In this paper, we present a mathematical model to explore the growth kinetics of CSC population both in vitro and in vivo. Our mathematical models and supporting experiments suggest that there exist non-linear growth kinetics of CSCs and negative feedback mechanisms to control the balance between the population of CSCs and that of non-stem cancer cells. The model predictions can help us explain a few long-standing questions in the field of cancer stem cell research, and can be potentially used to predict the efficicacy of anti-cancer therapy.

Lucena-Cacace, A., et al. (2018). "NAMPT Is a Potent Oncogene in Colon Cancer Progression that Modulates Cancer Stem Cell Properties and Resistance to Therapy through Sirt1 and PARP." Clin Cancer Res **24**(5): 1202-1215.

Purpose: Colorectal cancer is the second most common cancer in women and the third most common in men worldwide. However, despite current progress, many patients with advanced and metastatic tumors still die from the malignancy. Refractory disease often relies on nicotinamide adenine dinucleotide (NAD)-dependent mechanisms. NAD metabolism and a stable NAD regeneration circuit are required to maintain tissue homeostasis and metabolism. However, high levels of NAD confer therapy resistance to tumors.Experimental Design: Ectopic overexpression of nicotinamide phosphoribosil transferase (NAMPT) and shRNAs in colorectal cancer cell lines, tumorigenic and stemness properties and transcription measurement in culture and in vivo Transcriptional analysis in public databases. Therapeutic approaches.Results: NAMPT, the rate-limiting enzyme responsible for the highest source of physiologic NAD biosynthesis, increases tumorigenic properties and induces cancer stem cell-like properties through pathways that control stem cell signaling, thus enriching the cancer-initiating cell (CIC) population. Furthermore, NAMPT expression correlated with high levels of CIC-like cells in colon tumors directly extracted from patients, and transcription meta-analysis revealed that NAMPT is also a key factor that induces cancer stem pathways in colorectal cancer tumors. This effect is mediated by PARP and SIRT1. In addition, we report a novel NAMPT-driven signature that stratifies prognosis from high to low expression groups. The NAMPT signature contained SIRT1 and PARP1 levels as well as other cancer stem cell-related genes. Finally, NAMPT inhibition increased the sensitivity to apoptosis in both NAMPT-expressing cells and tumorspheres.Conclusions: NAMPT represents a novel therapeutic target in colon cancer progression and relapse, particularly the CIC subset of human colon cancers. Clin Cancer Res; 24(5); 1202-15. (c)2017 AACR.

Luo, Y. and D. Zhu (2014). "Combinatorial control of transgene expression by hypoxia-responsive promoter and microrna regulation for neural stem cell-based cancer therapy." Biomed Res Int **2014**: 751397.

Owing to their strong migratory capacity, tumor tropism, and tumor inhibitory effect, neural stem cells (NSCs) have recently emerged as one of the most attractive gene delivery vectors for cancer therapy. However, further animal studies found that proportional NSC vectors were distributed to nontarget organs after intravenous injection and the nonspecific transgene expression led to significant cytotoxic effects in these organs. Hence, an expression cassette that controls the transgene expression within NSC vectors in a tumor site-specific manner is desired. Considering hypoxia as a hallmark of tumor microenvironment, we have developed a novel NSC vector platform coupling transcriptional targeting with microRNA (miRNA) regulation for tumor hypoxia targeting. This combinatorial vector employed a hypoxia-responsive promoter and repeated targeting sequences of an miRNA that is enriched in NSCs but downregulated upon hypoxia induction to control the transgene expression. This resulted in significantly improved hypoxic selectivity over the use of a control vector without miRNA regulation. Thus, incorporating miRNA regulation into a transcriptional targeting vector adds an extra layer of security to prevent off-target transgene expression and should be useful for the development of NSC vectors with high targeting specifcity for cancer therapy.

Lytle, N. K., et al. (2018). "Stem cell fate in cancer growth, progression and therapy resistance." Nat Rev Cancer.

Although we have come a long way in our understanding of the signals that drive cancer growth, and how these signals can be targeted, effective control of this disease remains a key scientific and medical challenge. The therapy resistance and relapse that are commonly seen are driven in large part by the inherent heterogeneity within cancers that allows drugs to effectively eliminate some, but not all, malignant cells. Here, we focus on the fundamental drivers of this heterogeneity by examining emerging

evidence that shows that these traits are often controlled by the disruption of normal cell fate and aberrant adoption of stem cell signals. We discuss how undifferentiated cells are preferentially primed for transformation and often serve as the cell of origin for cancers. We also consider evidence showing that activation of stem cell programmes in cancers can lead to progression, therapy resistance and metastatic growth and that targeting these attributes may enable better control over a difficult disease.

Mader, E. K., et al. (2009). "Mesenchymal stem cell carriers protect oncolytic measles viruses from antibody neutralization in an orthotopic ovarian cancer therapy model." Clin Cancer Res **15**(23): 7246-7255.

PURPOSE: Preexisting antiviral antibodies in cancer patients can quickly neutralize oncolytic measles virus (MV) and decrease its antitumor potency. In contrast to "naked" viruses, cell-associated viruses are protected from antibody neutralization. Hence, we hypothesized that measles virotherapy of ovarian cancer in measles-immune mice might be superior if MV-infected mesenchymal stem cell (MSC) carriers are used. EXPERIMENTAL DESIGN: Antimeasles antibodies titers in ovarian cancer patients were determined. The protection of MV by MSC from antimeasles antibodies, the in vivo biodistribution profiles, and tumor infiltration capability of MSC were determined. Measles-naive or immune tumor-bearing mice were treated with naked virus or MSC-associated virus and mice survivals were compared. RESULTS: MSC transferred MV infection to target cells via cell-to-cell heterofusion and induced syncytia formation in the presence of high titers of antimeasles antibody, at levels that completely inactivated naked virus. Athymic mice bearing i.p. human SKOV3ip.1 ovarian tumor xenografts passively immunized with measles-immune human serum were treated with saline, naked MV, or MV-infected MSC. Bioluminescent and fluorescent imaging data indicated that i.p. administered MSC localized to peritoneal tumors, infiltrated into the tumor parenchyma, and transferred virus infection to tumors in measles naive and passively immunized mice. Survival of the measles-immune mice was significantly enhanced by treatment with MV-infected MSC. In contrast, survivals of passively immunized mice were not prolonged by treatment with naked virus or uninfected MSC. CONCLUSIONS: MSC should be used as carriers of MV for intraperitoneal virotherapy in measles-immune ovarian cancer patients.

Marini, F. C., et al. (1999). "Purging of contaminating breast cancer cells from hematopoietic stem cell grafts by adenoviral GAL-TEK gene therapy and magnetic antibody cell separation." Clin Cancer Res **5**(6): 1557-1568.

The presence of contaminating tumor cells in autologous bone marrow or peripheral blood stem cell (PB-SC) preparations increase the likelihood of relapse in women receiving transplants for metastatic breast cancer. We describe a new technique for purging breast cancer cells (BCCs) that combines two independent strategies: (a) the specific enrichment of CD34+ progenitor stem cells by magnetic antibody cell separation (MACS), and then (b) infection of the contaminating BCCs with a recombinant adGAL-TEK marker/suicide gene adenovirus (ad-v), followed by the addition of ganciclovir (GCV). Infection with this ad-v results in three to four times greater expression of ad-v-delivered reporter gene in BCCs than in CD34+ cells. In addition -2 h, -low multiplicity of infection (50:1) adGAL-TEK infections of BCC lines (MCF-7 and BT474) eradicated >99% of BCCs after 72 h of exposure to 20 microM GCV. However, exposure to both adenovirus and GCV at the MOIs and doses used had little effect on hematopoietic stem cells to form colonies in colony-forming unit assays. adGAL-TEK infection in our model system (10(3)-10(5) BCCs added into 10(7) HSCs) also resulted in the 3 to 5 log eradication of clonogenic BCCs after the addition of GCV. MACS enrichment/purification of CD34+ cells from PB-SC contaminated with 2 x 10(6) to 5 x 10(7) BCCs followed by adGAL-TEK infection and GCV addition resulted in 5-7-log depletion of clonogenic BCCs as well as enrichment of CD34+ progenitor cells to >98%, with the recovery of >70% of hematopoietic stem cells. This adenoviral purging system is so robust that poor MACS purification, resulting in 1.5-log depletion of BCCs, still permits excellent ad-v infection and BCC killing.

Marofi, F., et al. (2017). "Mesenchymal Stromal/Stem Cells: A New Era in the Cell-Based Targeted Gene Therapy of Cancer." Front Immunol **8**: 1770.

In recent years, in light of the promising potentials of mesenchymal stromal/stem cells (MSCs) for carrying therapeutic anticancer genes, a complete revisitation on old chemotherapy-based paradigms has been established. This review attempted to bring forward and introduce the novel therapeutic opportunities of using genetically engineered MSCs. The simplicities and advantages of MSCs for medical applications make them a unique and promising option in the case of cancer therapy. Some of the superiorities of using MSCs as therapeutic gene micro-carriers are the easy cell-extraction procedures and their abundant proliferation capacity in vitro without losing their main biological properties. Targeted therapy by using MSCs as the delivery vehicles of therapeutic genes is a new

approach in the treatment of various types of cancers. Some of the distinct properties of MSCs, such as tumor-tropism, non-immunogenicity, stimulatory effect on the anti-inflammatory molecules, inhibitory effect on inflammatory responses, non-toxicity against the normal tissues, and easy processes for the clinical use, have formed the basis of attention to MSCs. They can be easily used for the treatment of damaged or injured tissues, regenerative medicine, and immune disorders. This review focused on the drugability of MSCs and their potential for the delivery of candidate anticancer genes. It also briefly reviewed the vectors and methods used for MSC-mediated gene therapy of malignancies. Also, the challenges, limitations, and considerations in using MSCs for gene therapy of cancer and the new methods developed for resolution of these problems are reviewed.

Martinez-Climent, J. A., et al. (2000). "Chromosomal abnormalities in women with breast cancer after autologous stem cell transplantation are infrequent and may not predict development of therapy-related leukemia or myelodysplastic syndrome." Bone Marrow Transplant **25**(11): 1203-1208.

We determined prospectively the incidence of chromosomal abnormalities in patients with high-risk breast cancer (HRBC) after high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT), and correlated the cytogenetic abnormalities with the development of post-transplant myelodysplastic syndrome or acute myeloid leukemia (MDS/AML). From 1990 to 1999, 229 women with HRBC underwent ASCT. Cytogenetic analysis of bone marrow (BM) cells was performed 12-59 months after ASCT in 60 consecutive women uniformly treated with six courses of FAC/FEC followed by HDCT and ASCT. With a median follow-up of 36 months after ASCT, there were no cases of MDS/AML among the 229 patients. In the selected cohort of 60 patients, three (5%) showed clonal chromosomal abnormalities (two single trisomy X and one t (1;6)), whereas two additional patients showed non-clonal reciprocal translocations. Two of the patients with clonal aberrations had blood cytopenias as well as subtle dysplastic pictures in BM which were not classifiable as MDS according to the FAB criteria. Similar dysplastic features were also observed in four patients with normal karyotypes. All cytogenetic aberrations were transient and disappeared, except a +X detected by FISH in a residual cell population in one of the patients. Retrospective cytogenetic and FISH studies of samples obtained after six cycles of FAC/FEC and before transplant demonstrated no chromosomal abnormalities in any of the five patients with post-ASCT karyotypic changes. Early changes in karyotype detected in breast cancer patients following ASCT are transient and do not correlate with or predict development of MDS/AML. As these aberrations were not present before ASCT, they may be related to the HDCT regimen or transplant procedure rather than to the prior adjuvant therapy. Our results suggest that ASCT may be less likely to cause MDS or AML in breast cancer patients as compared to other malignancies. Bone Marrow Transplantation (2000) 25, 1203-1208.

Martin-Padura, I., et al. (2012). "Residual dormant cancer stem-cell foci are responsible for tumor relapse after antiangiogenic metronomic therapy in hepatocellular carcinoma xenografts." Lab Invest **92**(7): 952-966.

Hepatocellular carcinoma (HCC) is the fifth most common solid tumor and the third leading cause of cancer-related deaths. Currently available chemotherapeutic options are not curative due in part to tumor resistance to conventional therapies. We generated orthotopic HCC mouse models in immunodeficient NOD/SCID/IL2rgamma null mice by injection of human alpha-feto protein (hAFP)- and/or luciferase-expressing HCC cell lines and primary cells from patients, where tumor growth and spread can be accurately monitored in a non-invasive way. In this model, low-dose metronomic administration of cyclophosphamide (LDM-CTX) caused complete regression of the tumor mass. A significant increase in survival ($P<0.0001$), reduced aberrant angiogenesis and hyperproliferation, and decrease in the number of circulating tumor cells were found in LDM-CTX-treated animals, in comparison with untreated mice. Co-administration of LDM-CTX with anti-VEGF therapy further improved the therapeutic efficacy. However, the presence of residual circulating hAFP levels suggested that some tumor cells were still present in livers of treated mice. Immunohistochemistry revealed that those cells had a hAFP+/CD13+/PCNA- phenotype, suggesting that they were dormant cancer stem cells (CSC). Indeed, discontinuation of therapy resulted in tumor regrowth. Moreover, in-vitro LDM-CTX treatment reduced hepatosphere formation in both number and size, and the resulting spheres were enriched in CD13+ cells indicating that these cells were particularly resistant to therapy. Co-treatment of the CD13-targeting drug, bestatin, with LDM-CTX leads to slower tumor growth and a decreased tumor volume. Therefore, combining a CD13 inhibitor, which targets the CSC-like population, with LDM-CTX chemotherapy may be used to eradicate minimal residual disease and improve the treatment of liver cancer.

Masters, J. R., et al. (2008). "Prostate cancer stem cell therapy: hype or hope?" Prostate Cancer Prostatic Dis **11**(4): 316-319.

The stem cell concept of cancer suggests that each cancer contains a small fraction of stem cells responsible for the maintenance and progression of the disease. The implication of this concept is that by targeting and killing the cancer stem cells, it may be possible to improve survival or even cure the disease. Prostate cancer stem cell therapy is a valid goal to aim for, but there are massive hurdles to overcome, even if the concept is shown to be correct.

Mayank and V. Jaitak (2016). "Molecular docking study of natural alkaloids as multi-targeted hedgehog pathway inhibitors in cancer stem cell therapy." Comput Biol Chem **62**: 145-154.

Cancer is responsible for millions of deaths throughout the world every year. Increased understanding as well as advancements in the therapeutic aspect seems suboptimal to restrict the huge deaths associated with cancer. The major cause responsible for this is high resistance as well as relapse rate associated with cancers. Several evidences indicated that cancer stem cells (CSC) are mainly responsible for the resistance and relapses associated with cancer. Furthermore, agents targeting a single protein seem to have higher chances of resistance than multitargeting drugs. According to the concept of network model, partial inhibition of multiple targets is more productive than single hit agents. Thus, by fusing both the premises that CSC and single hit anticancer drugs, both are responsible for cancer related resistances and screened alkaloids for the search of leads having CSC targeting ability as well as the capability to modulating multiple target proteins. The in silico experimental data indicated that emetine and cortistatin have the ability to modulate hedgehog (Hh) pathway by binding to sonic hedgehog (Hh), smoothened (Smo) and Gli protein, involved in maintenance CSCs. Furthermore, solamargine, solasonine and tylophorine are also seems to be good lead molecules targeting towards CSCs by modulating Hh pathway. Except solamargine and solasonine, other best lead molecules also showed acceptable in silico ADME profile. The predicted lead molecules can be suitably modified to get multitargeting CSC targeting agent to get rid of associate resistances.

Meng, T., et al. (2016). "Multi-cycle chemotherapy with the glycolipid-like polymeric micelles evade cancer stem cell enrichment in breast cancer therapy." Oncotarget **7**(45): 72978-72989.

Multi-cycle chemotherapy is commonly used in the clinic, while the phenomena of enrichment of cancer stem cells (CSCs) and enhanced multi-drug resistance (MDR) are commonly involved. This research was designed for evaluating this successive administration. Chitosan oligosaccharide-g-stearic acid (CSOSA) polymer was used as the drug delivery system (DDS) to perform tri-cycle chemotherapy on a new tumor model induced by mammosphere cells. In vitro, on CSCs enriched mammospheres model, the doxorubicin-loaded CSOSA (CSOSA/DOX) displayed an improved growth inhibition effect measured by acid phosphatase assay (APH). While in vivo, the CSOSA/DOX micelles blocked tumor progression and led to a marked decrease of CSCs proportion as well as MDR capacity. What's more, the CSOSA/DOX helped decay the microenvironment and attenuate systemic side effects. We concluded that the CSOSA polymer could be a potential DDS for long-term multi-cycle chemotherapy in antitumor research.

Miekus, K. (2017). "The Met tyrosine kinase receptor as a therapeutic target and a potential cancer stem cell factor responsible for therapy resistance (Review)." Oncol Rep **37**(2): 647-656.

The MET tyrosine kinase receptor plays an important role during tumor development and progression being responsible for proliferation, morphogenetic transformation, cell motility and invasiveness. High expression of the MET receptor has been shown to correlate with increased tumor growth and metastasis, poor prognosis and resistance to radiotherapy. Moreover, MET expression and activation has been shown to be associated with therapy resistance. The occurrence of resistance to targeted therapy might be related to the presence of cancer stem cells (CSCs). CSCs are a subpopulation of cells in the tumor that possess the ability of self-renewal, clonogenicity, radioresistance and self-sustained protection from apoptosis. Recently, MET has been postulated as an essential factor supporting the functional stem cell phenotype in some tumors and as a CSC factor is believed to be responsible for therapy resistance. This review presents the results from recent studies identifying MET as a potential marker of CSCs and tumor initiating cells, demonstrating pivotal role of MET in supporting stem cell phenotype and indicating the role of MET in acquiring resistance to antitumor therapy.

Millar, B. C., et al. (1998). "The importance of CD34+/CD33- cells in platelet engraftment after intensive therapy for cancer patients given peripheral blood stem cell rescue." Bone Marrow Transplant **22**(5): 469-475.

The study was designed to determine whether the number of CD34+/CD33- cells given at autologous peripheral blood stem cell (PBSC) rescue after intensive therapy for cancer was a better predictor of

platelet engraftment than the total number of CD34+ cells infused. Comparison between the total number of CD34+ cells/kg infused with the number of CD34+/CD33- cells/kg infused showed that, generally, 2 x 10(6) total CD34+ cells contained 1.38 x 10(6) CD34+/CD33- cells. There was poor correlation between the number of CD34+/CD33- and CD34+/CD33+ cells in the graft (r = 0.332). Engraftment times for platelets and neutrophils were evaluated in 68 patients. There was no significant difference between the times for platelets to reach >25 x 10(9)/l or neutrophils to reach >0.5 x 10(9)/l among patients who received > or <2 x 10(6) total CD34+ cells or > or <1.38 x 10(6) CD34+/CD33- cells although the latter was consistently the better predictor. Platelet recovery to >50 x 10(9)/l and >100 x 10(9)/l was delayed significantly in patients who received <1.38 x 10(6) CD34+/CD33-/kg infused (P < 0.02 and P < 0.05, respectively). The number of CD34+/CD33- cells/kg infused was a stronger predictor of platelet recovery than the total number of CD34+ cells infused (P < 0.05 for platelets >50 or >100 x 10(9)/l). Although platelet recovery was delayed significantly in patients who had <4 x 10(4) granulocyte-macrophage colony-forming units (CFU-GM)/kg infused, the time delay between receipt of PBSCs and availability of the colony counts limits the use of this assay to patients who do not require stem cells to be given immediately. Our data suggest that the number of CD34+/CD33- cells given at PBSC rescue provide information about the quality of the graft necessary for long-term platelet engraftment. However, since the percentage of CD34+/CD33- cells shows considerable inter-patient variation, measurement of this cell population may be important in patients who experience poor stem cell mobilization or when a target dose of 2 x 10(6) total CD34+ cells/kg is not achieved.

Mohammadi, M., et al. (2016). "Mesenchymal stem cell: a new horizon in cancer gene therapy." Cancer Gene Ther **23**(9): 285-286.

Cancer is one of the main problems in public health worldwide. Despite rapid advances in the diagnosis and treatment of cancer, the efficacy of current treatment strategies is still limited. There are promising new results in animal models whereby mesenchymal stem cells (MSCs) can be used as vehicles for targeted therapies. The use of MSCs as therapeutic biological vehicles in cell therapy has several advantages, including immune-silence, tumor tropism, easy and rapid isolation, ex vivo expansion, multilineage differentiation and the capacity to deliver a number of therapeutic agents. Some studies have shown that the microenvironment of the tumor provides a preferential niche for homing and survival of MSCs. Here, we have highlighted various applications of MSCs in cancer gene therapy.

Moore, H. C., et al. (1999). "Autologous stem-cell transplant after conventional dose adjuvant chemotherapy for high-risk breast cancer: impact on the delivery of local-regional radiation therapy." Ann Oncol **10**(8): 929-936.

BACKGROUND: High-dose chemotherapy with autologous stem-cell transplantation is used increasingly in the treatment of poor-prognosis primary breast cancer. Because these patients may be cured with standard multimodality therapy, it is important to address both the efficacy of transplantation, and its effect on the delivery of standard treatments including local radiation therapy. PATIENTS AND METHODS: Patients with high risk primary breast cancer were treated with high-dose cyclophosphamide and thiotepa and stem-cell transplant following surgery and conventional-dose adjuvant chemotherapy. Outcome, including sites of failure and delivery of local radiation therapy, was assessed for 103 patients. RESULTS: Overall and disease-free survival rates at 18 months were 83% (+/- 4%) and 77% (+/- 4%) respectively. Twenty patients (19.4%) received radiation therapy prior to transplant. Of the remaining 83, 77 received radiation therapy after transplant. Overall, 5 (19.2%) of 26 first sites of recurrence were local alone. For patients receiving radiation prior to transplant, 3 of 7 (43%, 95% CI: 6%-80%) sites of first recurrence were local, while 2 of 19 (10.5%, 95% CI: 0%-24.5%) sites of first recurrence were local alone in patients receiving post-transplant radiation or no radiation. CONCLUSION: Transplantation does not appear to significantly compromise the delivery or outcome of local radiation therapy for primary breast cancer.

Moreno, M., et al. (2002). "Radiation therapy after high-dose chemotherapy with peripheral blood stem cell support for high-risk breast cancer." Am J Clin Oncol **25**(4): 347-353.

Multidisciplinary treatment in high-risk breast cancer improves survival and local control. The feasibility and patterns of failure after several induction and high-dose consolidation regimens of chemotherapy were evaluated in this study. Between November 1990 and January 1997, 65 patients with histologically proven breast cancer American Joint Committee on Cancer stages II-III with four or more axillary lymph nodes positive or locally advanced breast cancer underwent high-dose chemotherapy (HDC) with peripheral stem cell support after surgery and induction chemotherapy. All patients were subsequently treated with radiotherapy (up to total doses of 50-60 Gy), which included the ipsilateral

axilla and supraclavicular fossa and the chest wall or breast. A minimum follow-up period of 2 years from the completion of radiotherapy was required for analysis. Local control (LC), disease-free survival (DFS), overall survival (OS), and toxicity were evaluated. With a median follow-up of 62 months (range: 32-107 months), LC was 89%, and 5-year OS and DFS were 78% and 63%, respectively. Symptomatic pneumonitis developed in six patients (9%); only one patient had her radiotherapy interrupted because of hematologic toxicity. No treatment-related mortality was observed. Radiation therapy after HDC provides excellent local control rates without excessive toxicity. Delaying the start of irradiation until recovery from HDC does not seem to increase local failure rates.

Morgan, J., et al. (2010). "Substrate affinity of photosensitizers derived from chlorophyll-a: the ABCG2 transporter affects the phototoxic response of side population stem cell-like cancer cells to photodynamic therapy." Mol Pharm **7**(5): 1789-1804.

Photosensitizers (PS) synthesized with the aim of optimizing photodynamic therapy (PDT) of tumors do not always fulfill their potential when tested in vitro and in vivo in different tumor models. The ATP-dependent transporter ABCG2, a multidrug resistant pump expressed at variable levels in cancerous cells, can bind and efflux a wide range of structurally different classes of compounds including several PS used preclinically and clinically such as porphyrins and chlorins. ABCG2 may lower intracellular levels of substrate PS below the threshold for cell death in tumors treated by PDT, leaving resistant cells to repopulate the tumor. To determine some of the structural factors that affect substrate affinity of PS for ABCG2, we used an ABCG2-expressing cell line (HEK 293 482R) and its nonexpressing counterpart, and tyrosine kinase ABCG2 inhibitors in a simple flow cytometric assay to identify PS effluxed by the ABCG2 pump. We tested a series of conjugates of substrate PS with different groups attached at different positions on the tetrapyrrole macrocycle to examine whether a change in affinity for the pump occurred and whether such changes depended on the position or the structure/type of the attached group. PS without substitutions including pyropheophorbides and purpurinimides were generally substrates for ABCG2, but carbohydrate groups conjugated at positions 8, 12, 13, and 17 but not at position 3 abrogated ABCG2 affinity regardless of structure or linking moiety. At position 3, affinity was retained with the addition of iodobenzene, alkyl chains and monosaccharides, but not with disaccharides. This suggests that structural characteristics at position 3 may offer important contributions to requirements for binding to ABCG2. We examined several tumor cell lines for ABCG2 activity, and found that although some cell lines had negligible ABCG2 activity in bulk, they contained a small ABCG2-expressing side population (SP) thought to contain cells which are responsible for initiating tumor regrowth. We examined the relevance of the SP to PDT resistance with ABCG2 substrates in vitro and in vivo in the murine mammary tumor 4T1. We show for the first time in vivo that the substrate PS HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) but not the nonsubstrate PS HPPH-Gal (a galactose conjugate of HPPH) selectively preserved the SP which was primarily responsible for regrowth in vitro. The SP could be targeted by addition of imatinib mesylate, a tyrosine kinase inhibitor which inhibits the ATPase activity of ABCG2, and prevents efflux of substrates. A PDT resistant SP may be responsible for recurrences observed both preclinically and clinically. To prevent ABCG2 mediated resistance, choosing nonsubstrate PS or administering an ABCG2 inhibitor alongside a substrate PS might be advantageous when treating ABCG2-expressing tumors with PDT.

Moro, M., et al. (2012). "Patient-derived xenografts of non small cell lung cancer: resurgence of an old model for investigation of modern concepts of tailored therapy and cancer stem cells." J Biomed Biotechnol **2012**: 568567.

Current chemotherapy regimens have unsatisfactory results in most advanced solid tumors. It is therefore imperative to devise novel therapeutic strategies and to optimize selection of patients, identifying early those who could benefit from available treatments. Mouse models are the most valuable tool for preclinical evaluation of novel therapeutic strategies in cancer and, among them, patient-derived xenografts models (PDX) have made a recent comeback in popularity. These models, obtained by direct implants of tissue fragments in immunocompromised mice, have great potential in drug development studies because they faithfully reproduce the patient's original tumor for both immunohistochemical markers and genetic alterations as well as in terms of response to common therapeutics They also maintain the original tumor heterogeneity, allowing studies of specific cellular subpopulations, including their modulation after drug treatment. Moreover PDXs maintain at least some aspects of the human microenvironment for weeks with the complete substitution with murine stroma occurring only after 2-3 passages in mouse and represent therefore a promising model for studies of tumor-microenvironment interaction. This review summarizes our present knowledge on mouse preclinical cancer models, with a particular attention on patient-derived xenografts of non small cell lung

cancer and their relevance for preclinical and biological studies.

Motegi, A., et al. (2016). "Impact of Expression of CD44, a Cancer Stem Cell Marker, on the Treatment Outcomes of Intensity Modulated Radiation Therapy in Patients With Oropharyngeal Squamous Cell Carcinoma." Int J Radiat Oncol Biol Phys **94**(3): 461-468.

PURPOSE: To investigate the significance of CD44 protein expression on the treatment outcomes of radiation therapy in patients with oropharyngeal squamous cell carcinoma (OPSCC) with or without p16 protein expression in the tumor tissue. METHODS AND MATERIALS: We reviewed the medical records of 58 OPSCC patients who had undergone radiation therapy and examined the tumor tissue expressions of CD44 and p16 protein by immunohistochemical staining. The correlations between the expressions of these proteins and the patients' treatment outcomes were analyzed. RESULTS: The data of 58 consecutive OPSCC patients who had undergone definitive intensity modulated radiation therapy were analyzed. The male/female ratio was 55:3, and the median age was 64 years. The clinical stage of the disease was stage II in 7 patients, stage III in 5 patients, stage IVA in 35 patients, and stage IVB in 11 patients. Of the patients, 79% received additional induction and/or concurrent chemotherapy. The median follow-up duration was 34 months. The 3-year overall survival, progression-free survival (PFS) and locoregional control (LRC) rates of all the patients, regardless of the results of immunohistochemistry, were 73%, 64% and 76%, respectively. The PFS and LRC rates in the CD44(-) patients (86% and 93%, respectively) were significantly higher than those in the CD44(+) patients (57% and 70%, respectively). The PFS and LRC rates in the p16(+) patients (83% and 90%, respectively) were significantly higher than those in the p16(-) patients (45% and 61%, respectively). Patients who were CD44(-)/p16(+) showed the best LRC rates, and those who were CD44(+)/p16(-) showed the worst PFS and LRC rates among all the groups. CONCLUSIONS: Profiling of CD44 and p16 protein expressions by immunohistochemical staining is useful for predicting the treatment outcomes in patients with OPSCC undergoing definitive intensity modulated radiation therapy.

Muller, A. M., et al. (2016). "Hypoxia-targeted 131I therapy of hepatocellular cancer after systemic mesenchymal stem cell-mediated sodium iodide symporter gene delivery." Oncotarget **7**(34): 54795-54810.

Adoptively transferred mesenchymal stem cells (MSCs) home to solid tumors. Biologic features within the tumor environment can be used to selectively activate transgenes in engineered MSCs after tumor invasion. One of the characteristic features of solid tumors is hypoxia. We evaluated a hypoxia-based imaging and therapy strategy to target expression of the sodium iodide symporter (NIS) gene to experimental hepatocellular carcinoma (HCC) delivered by MSCs.MSCs engineered to express transgenes driven by a hypoxia-responsive promoter showed robust transgene induction under hypoxia as demonstrated by mCherry expression in tumor cell spheroid models, or radioiodide uptake using NIS. Subcutaneous and orthotopic HCC xenograft mouse models revealed significant levels of perchlorate-sensitive NIS-mediated tumoral radioiodide accumulation by tumor-recruited MSCs using 123I-scintigraphy or 124I-positron emission tomography. Functional NIS expression was further confirmed by ex vivo 123I-biodistribution analysis. Administration of a therapeutic dose of 131I in mice treated with NIS-transfected MSCs resulted in delayed tumor growth and reduced tumor perfusion, as shown by contrast-enhanced sonography, and significantly prolonged survival of mice bearing orthotopic HCC tumors. Interestingly, radioiodide uptake into subcutaneous tumors was not sufficient to induce therapeutic effects. Our results demonstrate the potential of using tumor hypoxia-based approaches to drive radioiodide therapy in non-thyroidal tumors.

Murakami, S., et al. (2015). "SRY and OCT4 Are Required for the Acquisition of Cancer Stem Cell-Like Properties and Are Potential Differentiation Therapy Targets." Stem Cells **33**(9): 2652-2663.

The acquisition of stemness is a hallmark of aggressive human hepatocellular carcinoma (hHCC). The stem cell marker OCT4 is frequently expressed in HCCs, and its expression correlates with those of putative cancer stem cell (CSC) markers and CSC properties. Here, we describe a novel mechanism of CSC maintenance by SRY through OCT4. We previously reported that Sry is involved in tumor malignancy in rodent HCCs. However, the oncogenic function of SRY in hHCCs is poorly understood. Ectopic expression of SRY increased multiple stem cell factors, including OCT4 and CD13. The OCT4 promoter contained SRY-binding sites that were directly activated by SRY. In HCC-derived cells, SRY knockdown decreased OCT4 expression and cancer stem-like phenotypes such as self-renewal, chemoresistance, and tumorigenicity. Conversely, OCT4 and SRY overexpression promoted cancer stem-like phenotypes. OCT4 knockdown in SRY clones downregulated the self-renewal capacity and

chemoresistance. These data suggest that SRY is involved in the maintenance of cancer stem-like characteristics through OCT4. Moreover, CSCs of HCC-derived cells differentiated into Tuj1-positive neuron-like cells by retinoic acid. Noteworthily, SRY was highly expressed in some hHCC patients. Taken together, our findings imply a novel therapeutic strategy against CSCs of hHCCs.

Nguyen, G. H., et al. (2011). "Cancer stem cell radioresistance and enrichment: where frontline radiation therapy may fail in lung and esophageal cancers." Cancers (Basel) **3**(1): 1232-1252.

Many studies have highlighted the role cancer stem cells (CSC) play in the development and progression of various types of cancer including lung and esophageal cancer. More recently, it has been proposed that the presence of CSCs affects treatment efficacy and patient prognosis. In reviewing this new area of cancer biology, we will give an overview of the current literature regarding lung and esophageal CSCs and radioresistance of CSC, and discuss the potential therapeutic applications of these findings.

Nichols, G., et al. (2002). "Therapy-related myelodysplastic syndrome after autologous stem cell transplantation for breast cancer." Leukemia **16**(9): 1673-1679.

Therapy-related myelodysplastic syndrome and acute myelogenous leukemia (t-MDS/AML) are serious complications of chemotherapy and radiotherapy for cancer. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) may be associated with an increased incidence of these complications. The frequency of t-MDS/AML after ASCT for breast cancer is uncertain. We reviewed our database of 379 consecutive breast cancer ASCT patients treated with alkylator-based chemotherapy, followed for a median of 1.52 years (range 0-8.97), with a median survival of 6.16 years. Three patients have developed tMDS/AML. The probability of developing this complication at 5 years is 0.032 in our series. We have used pathologic, cytogenetic and molecular methods to evaluate which portions of therapy may have predisposed to the development of this complication. Cytogenetic abnormalities were not found in the stem cell harvests of these patients by metaphase analysis or by fluorescence in situ hybridization (FISH). One patient demonstrated a clonal X chromosome inactivation pattern in her stem cell harvest, indicating pre-transplant chemotherapy may have been responsible for the development of her leukemia. As two of our patients developed this complication at greater than 4 years post-transplant, the number of cases may increase with longer follow-up. While the incidence appears to be low, further prospective and retrospective analysis will be necessary to determine which portions of therapy predispose to the development of t-MDS/AML in patients undergoing ASCT for treatment of breast cancer.

Oelmann, E., et al. (2002). "Early tandem high-dose ifosfamide, carboplatin, etoposide therapy with stem cell rescue for small-cell lung cancer: brief report on the results of a phase-I/II trial." Oncology **63**(3): 248-253.

OBJECTIVE: High-dose therapy (HDT) for small-cell lung cancer is experimental. Late intensification HDT for chemosensitive disease can increase the number and quality of remissions and prolong relapse-free survival, but has not yet shown impact on overall survival. This is possibly due to resistant residual disease. To overcome the development of resistance, we have tested early intensification tandem HDT. METHODS: We performed a phase-I/II trial using 1 conventional cycle of ifosfamide, carboplatin, etoposide (ICE) plus granulocyte colony-stimulating factor for stem cell recruitment followed by 2 cycles of high-dose ICE with rescue by CD34+ cell-enriched peripheral blood mononuclear cells. Dose escalation was performed for the 2 high-dose ICE cycles. Radiotherapy for limited disease was according to standard protocols. RESULTS: 17 patients were entered: 2 female patients; 15 male patients; median age 53 (range 36-65) years; 2 patients with limited disease, and 15 patients with extensive disease. We treated 4 patients at dose level 1, 11 patients at level 2, and 2 patients at level 3. The maximum tolerable dose was at level 2 with neuropathy being dose-limiting. Overall, toxicity was < or = grade 2 for all patients up to dose level 2 with hematotoxicity being grade 4 for all patients. There were 15 partial remissions (88%), 1 no change (6%), and 1 progressive disease (6%). Median time to progression was 7.9 months. Overall survival was 12.9 months (median). CONCLUSIONS: Early intensification with this protocol is feasible. Although a comparatively good response rate and median time to progression have been observed in this group dominated by patients with extensive disease, overall survival is short and no substantial long-term survival was found.

O'Flaherty, J. D., et al. (2012). "The cancer stem-cell hypothesis: its emerging role in lung cancer biology and its relevance for future therapy." J Thorac Oncol **7**(12): 1880-1890.

The cancer stem-cell (CSC) hypothesis suggests that there is a small subset of cancer cells that are responsible for tumor initiation and growth, possessing properties such as indefinite self-renewal, slow

replication, intrinsic resistance to chemotherapy and radiotherapy, and an ability to give rise to differentiated progeny. Through the use of xenotransplantation assays, putative CSCs have been identified in many cancers, often identified by markers usually expressed in normal stem cells. This is also the case in lung cancer, and the accumulated data on side population cells, CD133, CD166, CD44 and ALDH1 are beginning to clarify the true phenotype of the lung cancer stem cell. Furthermore, it is now clear that many of the pathways of normal stem cells, which guide cellular proliferation, differentiation, and apoptosis are also prominent in CSCs; the Hedgehog (Hh), Notch, and Wnt signaling pathways being notable examples. The CSC hypothesis suggests that there is a small reservoir of cells within the tumor, which are resistant to many standard therapies, and can give rise to new tumors in the form of metastases or relapses after apparent tumor regression. Therapeutic interventions that target CSC pathways are still in their infancy and clinical data of their efficacy remain limited. However Smoothened inhibitors, gamma-secretase inhibitors, anti-DLL4 antagonists, Wnt antagonists, and CBP/beta-catenin inhibitors have all shown promising anticancer effects in early studies. The evidence to support the emerging picture of a lung cancer CSC phenotype and the development of novel therapeutic strategies to target CSCs are described in this review.

Oosterhuis, J. W., et al. (2013). "Patient with two secondary somatic-type malignancies in a late recurrence of a testicular non-seminoma: illustration of potential and flaw of the cancer stem cell therapy concept." Int J Dev Biol **57**(2-4): 153-157.

Here, we report the case of a patient with a non-seminoma of the left testicle, with an intestinal-type adenocarcinoma and a low grade leiomyosarcoma in a late recurrence 19 years after initial diagnosis. The history of the patient, alive with disease 21 years after initial treatment, illustrates the potential and flaw of the cancer stem cell therapy concept. In addition, it is proposed that residual mature teratoma can be regarded as normalization of cancer due to embryonic patterning, and the development of a secondary somatic-type malignancy as failure of normalization.

Palau, J., et al. (2000). "[Cost of antibiotic therapy in neutropenic patients undergoing peripheral blood stem cell transplantation for breast cancer]." Rev Esp Quimioter **13**(2): 193-198.

The increase in pharmaceutical costs, especially for expensive procedures such as bone marrow transplants, has led to the study of the economic impact of febrile neutropenia in peripheral blood stem cell transplantation (PBSCT). We analyzed 89 consecutive patients with breast cancer who underwent PBSCT. All patients developed febrile neutropenia and were administered an empirical intravenous regimen based on the combination of piperacillin-tazobactam and amikacin. We analyzed the direct costs of this treatment and grouped them into drug acquisition cost, administration costs (cost of the additional material), and preparation costs (time employed for the preparation and administration of the drug). We found that the overall cost was $1,110, 65% of which corresponded to the initial therapy and the rest (35%) to the use of additional antibiotics. This higher cost was especially related to the use of vancomycin or teicoplanin (50%). The acquisition costs accounted for 90% of the overall treatment costs. Thirty-six patients (40%) did not need additional antibiotics and the cost in this group was less ($663). We concluded that knowledge of the costs of pharmacological therapy for infection in PBSCT is indispensable for the appropriate development of treatment units, especially in terms of optimizing resources and comparing different therapeutic or prophylactic approaches.

Pang, L. Y., et al. (2016). "Cyclooxygenase-2: A Role in Cancer Stem Cell Survival and Repopulation of Cancer Cells during Therapy." Stem Cells Int **2016**: 2048731.

Cyclooxygenase-2 (COX-2) is an inducible form of the enzyme that catalyses the synthesis of prostanoids, including prostaglandin E2 (PGE2), a major mediator of inflammation and angiogenesis. COX-2 is overexpressed in cancer cells and is associated with progressive tumour growth, as well as resistance of cancer cells to conventional chemotherapy and radiotherapy. These therapies are often delivered in multiple doses, which are spaced out to allow the recovery of normal tissues between treatments. However, surviving cancer cells also proliferate during treatment intervals, leading to repopulation of the tumour and limiting the effectiveness of the treatment. Tumour cell repopulation is a major cause of treatment failure. The central dogma is that conventional chemotherapy and radiotherapy selects resistant cancer cells that are able to reinitiate tumour growth. However, there is compelling evidence of an active proliferative response, driven by increased COX-2 expression and downstream PGE2 release, which contribute to the repopulation of tumours and poor patient outcome. In this review, we will examine the evidence for a role of COX-2 in cancer stem cell biology and as a mediator of tumour repopulation that can be molecularly targeted to overcome resistance to therapy.

Patel, S. A., et al. (2009). "Inflammatory mediators: Parallels between cancer biology and stem cell therapy." J Inflamm Res **2**: 13-19.

Inflammation encompasses diverse molecular pathways, and it is intertwined with a wide array of biological processes. Recently, there has been an upsurge of interest in the interactions between mediators of inflammation and other cells such as stem cells and cancer cells. Since tissue injuries are associated with the release of inflammatory mediators, it would be difficult to address this subject without considering the implications of their systemic effects. In this review, we discuss the effects of inflammatory reactions on stem cells and extrapolate on information pertaining to cancer biology. The discussion focuses on integrins and cytokines, and identifies the transcription factor, nuclear factor-kappa B (NFkappaB) as central to the inflammatory response. Since stem cell therapy has been proposed for type II diabetes mellitus, metabolic syndrome, pulmonary edema, these disorders are used as examples to discuss the roles of inflammatory mediators. We propose prospects for future research on targeting the NFkappaB signaling pathway. Finally, we explore the bridge between inflammation and stem cells, including neural stem cells and adult stem cells from the bone marrow. The implications of mesenchymal stem cells in regenerative medicine as pertaining to inflammation are vast based on their anti-inflammatory and immunosuppressive effects. Such features of stem cells offer great potential for therapy in graft-versus-host disease, conditions with a significant inflammatory component, and tissue regeneration.

Patel, S. R., et al. (2008). "Vaccinations in children treated with standard-dose cancer therapy or hematopoietic stem cell transplantation." Pediatr Clin North Am **55**(1): 169-186, xi.

Most children with cancer are immunocompromised during therapy and for a variable period after completion of therapy. They are at an increased risk of infections, including vaccine-preventable infections. There is a reduction in immunity to vaccine-preventable diseases after completion of standard-dose chemotherapy and after hematopoietic stem cell transplant. It is important to protect these children against vaccine-preventable diseases by reimmunization.

Patriarca, F., et al. (2003). "Prognostic significance of the detection of tumour cells in peripheral blood stem cell collections in stage II and III breast cancer patients treated with high-dose therapy." Bone Marrow Transplant **31**(9): 789-794.

The purpose of this study was to evaluate the incidence and extent of tumour cell contamination in bone marrow specimens and stem cell collections from 34 breast cancer patients undergoing high-dose therapy as adjuvant treatment, and to determine the prognostic significance for the clinical outcome. Tumour cell contamination was evaluated by flow cytometry using a double-colour test and an anti- Pan cytokeratin (CK) antibody. Two out of 34 (6%) baseline bone marrow specimens, none of seven marrow harvests and nine out of 32 aphereses (28%) mobilised from seven out of 27 patients (26%) contained CK+ cells. Tumour contamination was more frequent in patients with 10 or more involved lymph nodes and in those who received a shorter course of adjuvant chemotherapy before mobilisation. At a median follow-up of 43 months, 24 patients are in complete remission, whereas 10 patients experienced recurrence. Out of the 10 patients who relapsed, five (50%) had CK+ peripheral blood stem cell (PBSC) collections, whereas disease recurrence was seen in only two out of 24 (8%) patients who received CK- products (P=0.02). Moreover, CK+ PBSC collections were associated with a significantly shorter event-free survival and overall survival. CK+ collection is an unfavourable prognostic factor for patients treated with high-dose therapy. Whether the negative impact on clinical outcome depends on reinfusion of tumour cells or whether it simply indicates a larger disease extension is still unclear.

Petrelli, A., et al. (2015). "By promoting cell differentiation, miR-100 sensitizes basal-like breast cancer stem cells to hormonal therapy." Oncotarget **6**(4): 2315-2330.

Basal-like breast cancer is an aggressive tumor subtype with a poor response to conventional therapies. Tumor formation and relapse are sustained by a cell subset of Breast Cancer Stem Cells (BrCSCs). Here we show that miR-100 inhibits maintenance and expansion of BrCSCs in basal-like cancer through Polo-like kinase1 (Plk1) down-regulation. Moreover, miR-100 favors BrCSC differentiation, converting a basal like phenotype into luminal. It induces the expression of a functional estrogen receptor (ER) and renders basal-like BrCSCs responsive to hormonal therapy. The key role played by miR-100 in breast cancer free-survival is confirmed by the analysis of a cohort of patients' tumors, which shows that low expression of miR-100 is a negative prognostic factor and is associated with gene signatures of high grade undifferentiated tumors. Our findings indicate a new possible therapeutic strategy, which could make aggressive breast cancers responsive to standard treatments.

Prokopi, M., et al. (2014). "The Secret Role of microRNAs in Cancer Stem Cell Development and

Potential Therapy: A Notch-Pathway Approach." Front Oncol **4**: 389.

MicroRNAs (miRNAs) have been implicated in the development of some if not all cancer types and have been identified as attractive targets for prognosis, diagnosis, and therapy of the disease. miRNAs are a class of small non-coding RNAs (20-22 nt in length) that bind imperfectly to the 3'-untranslated region of target mRNA regulating gene expression. Aberrantly expressed miRNAs in cancer, sometimes known as oncomiRNAs, have been shown to play a major role in oncogenesis, metastasis, and drug resistance. Amplification of oncomiRNAs during cancer development correlates with the silencing of tumor suppressor genes; on the other hand, down-regulation of miRNAs has also been observed in cancer and cancer stem cells (CSCs). In both cases, miRNA regulation is inversely correlated with cancer progression. Growing evidence indicates that miRNAs are also involved in the metastatic process by either suppressing or promoting metastasis-related genes leading to the reduction or activation of cancer cell migration and invasion processes. In particular, circulating miRNAs (vesicle-encapsulated or non-encapsulated) have significant effects on tumorigenesis: membrane-particles, apoptotic bodies, and exosomes have been described as providers of a cell-to-cell communication system transporting oncogenic miRNAs from tumors to neighboring cells and distant metastatic sites. It is hypothesized that miRNAs control cancer development in a traditional manner, by regulating signaling pathways and factors. In addition, recent developments indicate a non-conventional mechanism of cancer regulation by stem cell reprograming via a regulatory network consisting of miRNAs and Wnt/beta-catenin, Notch, and Hedgehog signaling pathways, all of which are involved in controlling stem cell functions of CSCs. In this review, we focus on the role of miRNAs in the Notch-pathway and how they regulate CSC self-renewal, differentiation and tumorigenesis by direct/indirect targeting of the Notch-pathway.

Rachakatla, R. S., et al. (2008). "Combination treatment of human umbilical cord matrix stem cell-based interferon-beta gene therapy and 5-fluorouracil significantly reduces growth of metastatic human breast cancer in SCID mouse lungs." Cancer Invest **26**(7): 662-670.

Umbilical cord matrix stem (UCMS) cells that were engineered to express interferon-beta (IFN-beta) were transplanted weekly for three weeks into MDA 231 breast cancer xenografts bearing SCID mice in combination with 5-fluorouracil (5-FU). The UCMS cells were found within lung tumors but not in other tissues. Although both treatments significantly reduced MDA 231 tumor area in the SCID mouse lungs, the combined treatment resulted in a greater reduction in tumor area than by either treatment used alone. These results indicate that a combination treatment of UCMS-IFN-beta cells and 5-FU is a potentially effective therapeutic procedure for breast cancer.

Rameshwar, P. (2012). "Would cancer stem cells affect the future investment in stem cell therapy." World J Exp Med **2**(2): 26-29.

The common goal within the overwhelming interests in stem cell research is to safely translate the science to patients. Although there are various methods by which this goal can be reached, this editorial emphasizes the safety of mesenchymal stem cell (MSC) transplant and possible confounds by the growing information on cancer stem cells (CSCs). There are several ongoing clinical trials with MSCs and their interactions with CSCs need to be examined. The rapid knowledge on MSCs and CSCs has now collided with regards to the safe treatment of MSCs. The information discussed on MSCs can be extrapolated to other stem cells with similar phenotype and functions such as placenta stem cells. MSCs are attractive for cell therapy, mainly due to reduced ethical concerns, ease in expansion and reduced ability to be transformed. Also, MSCs can exert both immune suppressor and tissue regeneration simultaneously. It is expected that any clinical trial with MSCs will take precaution to ensure that the cells are not transformed. However, going forward, the different centers should be aware that MSCs might undergo oncogenic events, especially as undifferentiated cells or early differentiated cells. Another major concern for MSC therapy is their ability to promote tumor growth and perhaps, to protect CSCs by altered immune responses. These issues are discussed in light of a large number of undiagnosed cancers.

Rassi, H. (2009). "Stem cell therapy for hereditary breast cancer." Tsitol Genet **43**(3): 80-88.

Both hereditary and sporadic breast cancers may develop through dysregulation of self-renewal pathways of normal mammary stem cells. Networks of proto-oncogenes and tumor suppressors that control cancer cell proliferation also regulate stem cell self-renewal and possibly stem cell aging. Breast cancer susceptibility gene (BRCA1) is a nuclear phosphoprotein expressed in many nuclear processes, including stem cell regulator, DNA damage repair, recombination, transcription, ubiquitination, cell cycle checkpoint enforcement, and centrosome regulation. In this study, we report on recent advances on the functions of embryonic, fetal, and adult stem cell progenitors for hereditary breast cancer therapies. Several molecular targeting therapies are described by

activation and blocking distinct developmental signaling cascade elements, such as BRCA1, EGFR, hedgehog, Wnt/beta-catenin, and/or Notch pathways, which are frequently upregulated in cancer progenitor cells during the initiation and development of breast cancer.

Reagan, M. R., et al. (2012). "Stem Cell Implants for Cancer Therapy: TRAIL-Expressing Mesenchymal Stem Cells Target Cancer Cells In Situ." J Breast Cancer **15**(3): 273-282.

PURPOSE: Tumor-specific delivery of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), an apoptosis-inducing peptide, at effective doses remains challenging. Herein we demonstrate the utility of a scaffold-based delivery system for sustained therapeutic cell release that capitalizes on the tumor-homing properties of mesenchymal stem cells (MSCs) and their ability to express genetically-introduced therapeutic genes. METHODS: Implants were formed from porous, biocompatible silk scaffolds seeded with full length TRAIL-expressing MSCs (FLT-MSCs). under a doxycycline inducible promoter. In vitro studies with FLT-MSCs demonstrated TRAIL expression and antitumor effects on breast cancer cells. Next, FLT-MSCs were administered to mice using three administration routes (mammary fat pad co-injections, tail vein injections, and subcutaneous implantation on scaffolds). RESULTS: In vitro cell-specific bioluminescent imaging measured tumor cell specific growth in the presence of stromal cells and demonstrated FLT-MSC inhibition of breast cancer growth. FLT-MSC implants successfully decreased bone and lung metastasis, whereas liver metastasis decreased only with tail vein and co-injection administration routes. Average tumor burden was decreased when doxycycline was used to induce TRAIL expression for co-injection and scaffold groups, as compared to controls with no induced TRAIL expression. CONCLUSION: This implant-based therapeutic delivery system is an effective and completely novel method of anticancer therapy and holds great potential for clinical applications.

Reed, E., et al. (2003). "Occult tumor cells detected in autologous blood stem cell harvests have no impact on 5 year outcomes for breast cancer patients with 4-9 positive nodes treated with adjuvant high-dose therapy and stem cell transplantation." Bone Marrow Transplant **31**(7): 571-574.

Breast cancer cells have been detected in autologous blood stem cell collections of early stage breast cancer patients, but their clinical significance is undefined. From October 1993 to August 1998, 32 consecutive Stage II breast cancer patients with 4-9-positive nodes underwent stem cell apheresis. The patients were treated with cyclophosphamide 1.75 gm/m (2), etoposide 400 mg/m (2) and cisplatin 50 mg/m (2) daily for 3 days, followed by infusion of the autologous cells. Cytospins of cells from each apheresis collections and from an aliquot of three pooled collections were examined for cytokeratin expression using an immunocytochemical assay. The cells were considered positive for tumor if at least one cell with tumor morphology stained positively for cytokeratin. Negative aliquots were confirmed with RT-PCR. Six patients (19%) had positive collections. In total, 24 patients (75%) were disease free a median of 61 (30-86) months after transplant. Eight patients relapsed at a median of 17 (8-27) months after transplant. Four of the disease-free patients and two of the relapsed patients had positive apheresis collections. There was no significant correlation between the presence of detectable tumor cells in the graft product and outcome.

Reisner, Y. and H. Segall (1995). "Hematopoietic stem cell transplantation for cancer therapy." Curr Opin Immunol **7**(5): 687-693.

Bone marrow transplantation has become well established in the treatment of malignant disorders. High-dose chemotherapy with hematopoietic stem cell support is widely used for most hematological malignancies, as well as for some solid tumors. In the light of recent developments in blood progenitor cell harvest, there have been clinical trials with autologous and allogeneic transplants. In particular, the availability of large numbers of blood stem cells, mobilized by granulocyte colony-stimulating factor and collected by leukapheresis, has made it possible to overcome histocompatibility barriers in HLA-mismatched leukemia patients. Other recent developments include new methods for blood progenitor cells mobilization and ex vivo expansion, the use of umbilical cord blood as an alternative source of stem cells, and molecular techniques that may, in the future, provide other modalities of purging tumor cells from autologous grafts.

Richman, C. M., et al. (1999). "Dosimetry-based therapy in metastatic breast cancer patients using 90Y monoclonal antibody 170H.82 with autologous stem cell support and cyclosporin A." Clin Cancer Res **5**(10 Suppl): 3243s-3248s.

Radioimmunoconjugates of 170H.82 (m170), a panadenocarcinoma monoclonal antibody, are effective for imaging primary and metastatic breast cancer. To evaluate m170 as a targeting agent for therapy, we developed (111)In- and 90Y-2-iminothiolane-2-[p-(bromoacetamido)benzyl]-1,4,7,10 tetraazacyclododecane-N,N',N",N"'-tetraacetic acid-m170 immunoconjugates with 99% purity by

molecular sieving and immunoreactivity comparable to unmodified antibody. (111)In-m170 pharmacokinetic studies were performed prior to each therapy to determine the maximum dose of 90Y-m170 that could be administered without exceeding a limit of 800 rad to the liver, lungs, or kidneys or 250 rad to the whole body or bone marrow for each of three cycles of treatment. Peripheral blood stem cells (PBSCs) were harvested and cyclosporin A (5 mg/kg twice daily) was administered as strategies to ameliorate myelosuppression and prevent the development of HAMA, respectively. An (111)In imaging/pharmacokinetic study was performed, and the 90Y dose was calculated and administered. The liver was the 90Y dose-limiting organ. The mean and range of calculated doses (in rad/mCi) for the five patients evaluated were as follows: whole body, 2.3 (2.1-2.4); liver, 17.8 (12.7-22.2); lung, 6.4 (4.8-7.2); kidney, 6.9 (6.3-11.5); marrow, 3.6 (1.9-4.4); and tumors (n = 25), 71.5 (14.1-141.5). Of the three patients treated, with doses of 37, 54, and 57 mCi of 90Y, one had a partial response, one had measurable tumor reduction but less than a partial response, and one had stable disease for more than 1 month. PBSCs prevented prolonged myelosuppression. The therapeutic responses, coupled with an absence, thus far, of significant adverse sequelae, suggest that this dosimetry-based approach combined with PBSCs may lead to effective therapy when higher 90Y doses are reached.

Rizzieri, D. A., et al. (1999). "Prognostic and predictive factors for patients with metastatic breast cancer undergoing aggressive induction therapy followed by high-dose chemotherapy with autologous stem-cell support." J Clin Oncol **17**(10): 3064-3074.

PURPOSE: We performed a retrospective review to determine predictive and prognostic factors in patients with metastatic breast cancer who received induction therapy, and, if they responded to treatment, high-dose chemotherapy. PATIENTS AND METHODS: Patients with metastatic breast cancer received induction therapy with doxorubicin, fluorouracil, and methotrexate (AFM). Partial responders then received immediate high-dose chemotherapy, whereas those who achieved complete remission were randomized to immediate or delayed high-dose chemotherapy with hematopoietic stem-cell support. We performed a retrospective review of data from these patients and used Cox proportional hazards regression models for analyses. RESULTS: The overall response rate for the 425 patients enrolled was 74% (95% confidence interval, 70% to 78%). Multivariate analysis of data from all 425 patients revealed that positive estrogen receptor status (P =.0041), smaller metastatic foci (</= 2 v > 2 cm) (P =. 0165), a longer disease-free interval from initial diagnosis to diagnosis of metastases (</= 2 v > 2 years) (P =.0051), and prior treatment with tamoxifen (P =.0152) were good prognostic signs for overall survival. Patients who had received prior adjuvant therapy (P =.0001) and those who developed liver metastases (P =.0001) had decreased long-term survival. In the subgroup of responders to AFM induction, multivariate analysis showed that those with visceral metastases did less well (P =.0006), as did patients who had received prior adjuvant therapy (P =.0023). However, those who had received tamoxifen therapy in the adjuvant setting did better (P =. 0143). CONCLUSION: The chance for long-term remission with induction therapy with AFM and high-dose chemotherapy is increased for hormone receptor positive-patients with nonvisceral metastases who have not received prior adjuvant chemotherapy and have long disease-free intervals.

Rodova, M., et al. (2012). "Sonic hedgehog signaling inhibition provides opportunities for targeted therapy by sulforaphane in regulating pancreatic cancer stem cell self-renewal." PLoS One **7**(9): e46083.

Dysregulation of the sonic hedgehog (Shh) signaling pathway has been associated with cancer stem cells (CSC) and implicated in the initiation of pancreatic cancer. Pancreatic CSCs are rare tumor cells characterized by their ability to self-renew, and are responsible for tumor recurrence accompanied by resistance to current therapies. The lethality of these incurable, aggressive and invasive pancreatic tumors remains a daunting clinical challenge. Thus, the objective of this study was to investigate the role of Shh pathway in pancreatic cancer and to examine the molecular mechanisms by which sulforaphane (SFN), an active compound in cruciferous vegetables, inhibits self-renewal capacity of human pancreatic CSCs. Interestingly, we demonstrate here that Shh pathway is highly activated in pancreatic CSCs and plays important role in maintaining stemness by regulating the expression of stemness genes. Given the requirement for Hedgehog in pancreatic cancer, we investigated whether hedgehog blockade by SFN could target the stem cell population in pancreatic cancer. In an in vitro model, human pancreatic CSCs derived spheres were significantly inhibited on treatment with SFN, suggesting the clonogenic depletion of the CSCs. Interestingly, SFN inhibited the components of Shh pathway and Gli transcriptional activity. Interference of Shh-Gli signaling significantly blocked SFN-induced inhibitory effects demonstrating the requirement of an active pathway for the growth of pancreatic CSCs. SFN also inhibited downstream targets of Gli transcription by suppressing the expression of pluripotency maintaining factors (Nanog

and Oct-4) as well as PDGFRalpha and Cyclin D1. Furthermore, SFN induced apoptosis by inhibition of BCL-2 and activation of caspases. Our data reveal the essential role of Shh-Gli signaling in controlling the characteristics of pancreatic CSCs. We propose that pancreatic cancer preventative effects of SFN may result from inhibition of the Shh pathway. Thus Sulforaphane potentially represents an inexpensive, safe and effective alternative for the management of pancreatic cancer.

Rovida, E., et al. (2014). "The metabolically-modulated stem cell niche: a dynamic scenario regulating cancer cell phenotype and resistance to therapy." Cell Cycle **13**(20): 3169-3175.

This Perspective addresses the interactions of cancer stem cells (CSC) with environment which result in the modulation of CSC metabolism, and thereby of CSC phenotype and resistance to therapy. We considered first as a model disease chronic myeloid leukemia (CML), which is triggered by a well-identified oncogenetic protein (BCR/Abl) and brilliantly treated with tyrosine kinase inhibitors (TKi). However, TKi are extremely effective in inducing remission of disease, but unable, in most cases, to prevent relapse. We demonstrated that the interference with cell metabolism (oxygen/glucose shortage) enriches cells exhibiting the leukemia stem cell (LSC) phenotype and, at the same time, suppresses BCR/Abl protein expression. These LSC are therefore refractory to the TKi Imatinib-mesylate, pointing to cell metabolism as an important factor controlling the onset of TKi-resistant minimal residual disease (MRD) of CML and the related relapse. Studies of solid neoplasias brought another player into the control of MRD, low tissue pH, which often parallels cancer growth and progression. Thus, a 3-party scenario emerged for the regulation of CSC/LSC maintenance, MRD induction and disease relapse: the "hypoxic" versus the "ischemic" vs. the "acidic" environment. As these environments are unlikely constrained within rigid borders, we named this model the "metabolically-modulated stem cell niche."

Sakamoto, N., et al. (2017). "Non-coding RNAs are promising targets for stem cell-based cancer therapy." Noncoding RNA Res **2**(2): 83-87.

The term "non-coding RNA" (ncRNA) is generally used to indicate RNA that does not encode a protein and includes several classes of RNAs, such as microRNA and long non-coding RNA. Several lines of evidence suggest that ncRNAs appear to be involved in a hidden layer of biological procedures that control various levels of gene expression in physiology and development including stem cell biology. Stem cells have recently constituted a revolution in regenerative medicine by providing the possibility of generating suitable cell types for therapeutic use. Here, we review the recent progress that has been made in elaborating the interaction between ncRNAs and tissue/cancer stem cells, discuss related technical and biological challenges, and highlight plausible solutions to surmount these difficulties. This review particularly emphasises the involvement of ncRNAs in stem cell biology and in vivo modulation to treat and cure specific pathological disorders especially in cancer. We believe that a better understanding of the molecular machinery of ncRNAs as related to pluripotency, cellular reprogramming, and lineage-specific differentiation is essential for progress of cancer therapy.

Salim, E. I., et al. (2016). "Expression Patterns of Cancer Stem Cell Markers During Specific Celecoxib Therapy in Multistep Rat Colon Carcinogenesis Bioassays." Asian Pac J Cancer Prev **17**(3): 1023-1035.

The purpose of this study was to investigate the role of colon cancer stem cells (CSCs) during chemicallyinduced rat multi-step colon carcinogenesis with or without the treatment with a specific cyclooxygenase-2 inhibitor drug (celecoxib). Two experiments were performed, the first, a short term 12 week colon carcinogenesis bioassay in which only surrogate markers for colon cancer, aberrant crypt foci (ACF) lesions, were formed. The other experiment was a medium term colon cancer rat assay in which tumors had developed after 32 weeks. Treatment with celecoxib lowered the numbers of ACF, as well as the tumor volumes and multiplicities after 32 weeks. Immunohistochemical proliferating cell nuclear antigen (PCNA) labeling indexes LI (%) were downregulated after treatment by celecoxib. Also different cell surface antigens known to associate with CSCs such as the epithelial cell adhesion molecule (EpCAM), CD44 and CD133 were compared between the two experiments and showed differential expression patterns depending on the stage of carcinogenesis and treatment with celecoxib. Flow cytometric analysis demonstrated that the numbers of CD133 cells were increased in the colonic epithelium after 12 weeks while those of CD44 but not CD133 cells were increased after 32 weeks. Moreover, aldehyde dehydrogenase-1 activity levels in the colonic epithelium (a known CSC marker) detected by ELISA assay were found down-regulated after 12 weeks, but were up-regulated after 32 weeks. The data have also shown that the protective effect of celecoxib on these specific markers and populations of CSCs and on other molecular processes such as apoptosis targeted by this drug may vary depending on the genetic and phenotypic stages of carcinogenesis. Therefore, uncovering these distinction roles of CSCs

during different phases of carcinogenesis and during specific treatment could be useful for targeted therapy.

Scherwath, A., et al. (2006). "Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects." Ann Oncol **17**(3): 415-423.

BACKGROUND: Studies on cognitive functioning in breast cancer patients point out that a subset of women exhibit chemotherapy-related neuropsychological impairment. Thereby, high-dose therapy may elevate the risk of cognitive dysfunctions. The primary purpose of the study was to evaluate the impact of high-dose versus standard-dose chemotherapy on the late neuropsychological outcome in randomized assigned high-risk breast cancer survivors. Next to focusing prevalence, function specificity and extent of cognitive impairment, the question as to whether doses-dependent group differences occur was investigated. PATIENTS AND METHODS: Twenty-four high-dose and 23 standard-dose patients 5 years, on average, after treatment underwent a comprehensive neuropsychological assessment. In addition, 29 early-stage breast cancer patients matched for age, education and time since treatment were recruited as a comparison group. RESULTS: Global cognitive impairment was observed in 8% of high-dose versus 13% of standard-dose compared with 3% of early-stage breast cancer patients. Compared with normative data, all patient groups performed worse on one attention subtest measuring the simple reaction time ($P < 0.001$ in each case). By contrast, no significant between-group differences on the late neuropsychological outcome were found. CONCLUSIONS: Five years after treatment, standard-dose patients were slightly, but not significantly, more impaired in cognitive performance than high-dose patients.

Sehl, M., et al. (2011). "Extinction models for cancer stem cell therapy." Math Biosci **234**(2): 132-146.

Cells with stem cell-like properties are now viewed as initiating and sustaining many cancers. This suggests that cancer can be cured by driving these cancer stem cells to extinction. The problem with this strategy is that ordinary stem cells are apt to be killed in the process. This paper sets bounds on the killing differential (difference between death rates of cancer stem cells and normal stem cells) that must exist for the survival of an adequate number of normal stem cells. Our main tools are birth-death Markov chains in continuous time. In this framework, we investigate the extinction times of cancer stem cells and normal stem cells. Application of extreme value theory from mathematical statistics yields an accurate asymptotic distribution and corresponding moments for both extinction times. We compare these distributions for the two cell populations as a function of the killing rates. Perhaps a more telling comparison involves the number of normal stem cells NH at the extinction time of the cancer stem cells. Conditioning on the asymptotic time to extinction of the cancer stem cells allows us to calculate the asymptotic mean and variance of NH. The full distribution of NH can be retrieved by the finite Fourier transform and, in some parameter regimes, by an eigenfunction expansion. Finally, we discuss the impact of quiescence (the resting state) on stem cell dynamics. Quiescence can act as a sanctuary for cancer stem cells and imperils the proposed therapy. We approach the complication of quiescence via multitype branching process models and stochastic simulation. Improvements to the tau-leaping method of stochastic simulation make it a versatile tool in this context. We conclude that the proposed therapy must target quiescent cancer stem cells as well as actively dividing cancer stem cells. The current cancer models demonstrate the virtue of attacking the same quantitative questions from a variety of modeling, mathematical, and computational perspectives.

Sehl, M. E., et al. (2009). "Differential destruction of stem cells: implications for targeted cancer stem cell therapy." Cancer Res **69**(24): 9481-9489.

Cancer stem cells represent a novel therapeutic target. The major challenge in targeting leukemic stem cells (LSC) is finding therapies that largely spare normal hematopoietic stem cells (HSC) while eradicating quiescent LSCs. We present a mathematical model to predict how selective a therapy must be to ensure that enough HSCs survive when LSCs have been eradicated. Stem cell population size is modeled as a birth-death process. This permits comparison of LSC and HSC eradication times under therapy and calculation of the number of HSCs at the time of LSC eradication for varied initial population sizes and stem cell death rates. We further investigate the effects of LSC quiescence and resistance mutations on our predictions. From a clinical point of view, our models suggest criteria by which cancer stem cell therapy safety can be assessed. We anticipate that in conjunction with experimental observation of cancer stem cell killing rates, our results will be useful in screening targeted therapies for both hematologic and solid tumor malignancies.

Sell, S. (2004). "Stem cell origin of cancer and differentiation therapy." Crit Rev Oncol Hematol **51**(1): 1-28.

Our forefathers in pathology, on observing cancer tissue under the microscope in the mid-19th century, noticed the similarity between embryonic tissue and cancer, and suggested that tumors arise from embryo-like cells [Recherches dur le Traitement du Cancer, etc. Paris. (1829); Editoral Archiv fuer pathologische Anatomie und Physiologie und fuer klinische Medizin 8 (1855) 23]. The concept that adult tissues contain embryonic remnants that generally lie dormant, but that could be activated to become cancer was later formalized by Cohnheim [Path. Anat. Physiol. Klin. Med. 40 (1867) 1-79; Virchows Arch. 65 (1875) 64] and Durante [Arch. Memori ed Osservazioni di Chirugia Practica 11 (1874) 217-226], as the "embryonal rest" theory of cancer. An updated version of the embryonal rest theory of cancer is that cancers arise from tissue stem cells in adults. Analysis of the cellular origin of carcinomas of different organs indicates that there is, in each instance, a determined stem cell required for normal tissue renewal that is the most likely cell of origin of carcinomas [Lab. Investig. 70 (1994) 6-22]. In the present review, the nature of normal stem cells (embryonal, germinal and somatic) is presented and their relationships to cancer are further expanded. Cell signaling pathways shared by embryonic cells and cancer cells suggest a possible link between embryonic cells and cancer cells. Wilm's tumors (nephroblastomas) and neuroblastomas are presented as possible tumors of embryonic rests in children. Teratocarcinoma is used as the classic example of the totipotent cancer stem cell which can be influenced by its environment to differentiate into a mature adult cell. The observation that "promotion" of an epidermal cancer may be accomplished months or even years after the initial exposure to carcinogen ("initiation"), implies that the original carcinogenic event occurs in a long-lived epithelial stem cell population. The cellular events during hepatocarcinogenesis illustrate that cancers may arise from cells at various stages of differentiation in the hepatocyte lineage. Examples of genetic mutations in epithelial and hematopoietic cancers show how specific alterations in gene expression may be manifested as maturation arrest of a cell lineage at a specific stage of differentiation. Understanding the signals that control normal development may eventually lead us to insights in treating cancer by inducing its differentiation (differentiation therapy). Retinoid acid (RA) induced differentiation therapy has acquired a therapeutic niche in treatment of acute promyelocytic leukemia and the ability of RA to prevent cancer is currently under examination.

Shao, L., et al. (2013). "Hematopoietic stem cell senescence and cancer therapy-induced long-term bone marrow injury." Transl Cancer Res **2**(5): 397-411.

Due to improvements in early detection and treatment of cancer, the number of long-term cancer survivors is increasing. Unfortunately, these survivors are at increased risk for developing cancer treatment-related late effects, including ionizing radiation (IR)- and chemotherapy-induced long-term bone marrow (LT-BM) injury. Because LT-BM injury can deteriorate over time or after the patients receiving additional cancer treatment or undergoing autologous BM transplantation, it may eventually lead to the development of hypoplastic anemia or myelodysplastic syndrome. This review is to provide a survey of some of these recent findings regarding the underlying mechanisms by which IR and chemotherapy cause LT-BM injury. Particularly, we will highlight the discoveries of the role of reactive oxygen species in regulating HSC self-renewal and the role of oxidative stress in mediating IR- and chemotherapy-induced HSC senescence and LT-BM injury. These discoveries may lead to the development of new therapeutic strategies that have the potential to reduce the late adverse effects of conventional cancer therapy on the hematopoietic system in long-term cancer survivors.

Sharkis, S. J., et al. (2012). "Pluripotent stem cell-based cancer therapy: promise and challenges." Sci Transl Med **4**(127): 127ps129.

The development of induced pluripotent stem cell (iPSC) technology has generated enthusiasm about the therapeutic potential of these cells for treating a variety of diseases. However, the evidence that they actually will be clinically useful is limited. Here, we discuss the potential therapeutic applications of iPSCs for treating cancer and other diseases and highlight the current barriers restricting their use.

Sharma, B. and R. K. Singh (2011). "Emerging candidates in breast cancer stem cell maintenance, therapy resistance and relapse." J Carcinog **10**: 36.

Therapy resistance is a major concern while treating breast cancer. Various mechanisms have been proposed, but so far nothing has been able to effectively address this problem. Accumulating evidences suggest that a subset of cancer cells provides survival benefits to the tumor and are responsible for therapy resistance and relapse of cancer. These so called the cancer stem cells, are known to be regulated by several pathways. Evidences shows that the tumor microenvironment plays a crucial role in maintaining the cancer stem cell pool. Signaling within the tumor is modulated by surrounding cells which secrete signals favoring tumor growth and metastasis. In breast cancer, the cancer

stem cells have recently been reported to be influenced by tumor microenvironment via cytokines which act as chemoattractants for leukocytes. This review elucidates the emerging role of chemokine receptor and receptor activator of NFkappaB (RANK) ligand/RANK signaling pathways in mediating therapy resistance of breast cancer by maintaining the cancer stem cell pool.

Sharp, T. E., 3rd and J. C. George (2014). "Stem cell therapy and breast cancer treatment: review of stem cell research and potential therapeutic impact against cardiotoxicities due to breast cancer treatment." Front Oncol **4**: 299.

A new problem has emerged with the ever-increasing number of breast cancer survivors. While early screening and advances in treatment have allowed these patients to overcome their cancer, these treatments often have adverse cardiovascular side effects that can produce abnormal cardiovascular function. Chemotherapeutic and radiation therapy have both been linked to cardiotoxicity; these therapeutics can cause a loss of cardiac muscle and deterioration of vascular structure that can eventually lead to heart failure (HF). This cardiomyocyte toxicity can leave the breast cancer survivor with a probable diagnosis of dilated or restrictive cardiomyopathy (DCM or RCM). While current HF standard of care can alleviate symptoms, other than heart transplantation, there is no therapy that replaces cardiac myocytes that are killed during cancer therapies. There is a need to develop novel therapeutics that can either prevent or reverse the cardiac injury caused by cancer therapeutics. These new therapeutics should promote the regeneration of lost or deteriorating myocardium. Over the last several decades, the therapeutic potential of cell-based therapy has been investigated for HF patients. In this review, we discuss the progress of pre-clinical and clinical stem cell research for the diseased heart and discuss the possibility of utilizing these novel therapies to combat cardiotoxicity observed in breast cancer survivors.

Sharrow, A. C., et al. (2016). "Characterization of aldehyde dehydrogenase 1 high ovarian cancer cells: Towards targeted stem cell therapy." Gynecol Oncol **142**(2): 341-348.

OBJECTIVE: The cancer stem cell (CSC) paradigm hypothesizes that successful clinical eradication of CSCs may lead to durable remission for patients with ovarian cancer. Despite mounting evidence in support of ovarian CSCs, their phenotype and clinical relevance remain unclear. We and others have found high aldehyde dehydrogenase 1 (ALDH (high)) expression in a variety of normal and malignant stem cells, and sought to better characterize ALDH (high) cells in ovarian cancer. METHODS: We compared ALDH (high) to ALDH (low) cells in two ovarian cancer models representing distinct subtypes: FNAR-C1 cells, derived from a spontaneous rat endometrioid carcinoma, and the human SKOV3 cell line (described as both serous and clear cell subtypes). We assessed these populations for stem cell features then analyzed expression by microarray and qPCR. RESULTS: ALDH (high) cells displayed CSC properties, including: smaller size, quiescence, regenerating the phenotypic diversity of the cell lines in vitro, lack of contact inhibition, nonadherent growth, multi-drug resistance, and in vivo tumorigenicity. Microarray and qPCR analysis of the expression of markers reported by others to enrich for ovarian CSCs revealed that ALDH (high) cells of both models showed downregulation of CD24, but inconsistent expression of CD44, KIT and CD133. However, the following druggable targets were consistently expressed in the ALDH (high) cells from both models: mTOR signaling, her-2/neu, CD47 and FGF18/FGFR3. CONCLUSIONS: Based on functional characterization, ALDH (high) ovarian cancer cells represent an ovarian CSC population. Differential gene expression identified druggable targets that have the potential for therapeutic efficacy against ovarian CSCs from multiple subtypes.

Shen, S., et al. (2016). "Nanomedicine-mediated cancer stem cell therapy." Biomaterials **74**: 1-18.

Circumstantial evidence suggests that most tumours are heterogeneous and contain a small population of cancer stem cells (CSCs) that exhibit distinctive self-renewal, proliferation and differentiation capabilities, which are believed to play a crucial role in tumour progression, drug resistance, recurrence and metastasis in multiple malignancies. Given that the existence of CSCs is a primary obstacle to cancer therapy, a tremendous amount of effort has been put into the development of anti-CSC strategies, and several potential approaches to kill therapeutically-resistant CSCs have been explored, including inhibiting ATP-binding cassette transporters, blocking essential signalling pathways involved in self-renewal and survival of CSCs, targeting CSCs surface markers and destroying the tumour microenvironment. Meanwhile, an increasing number of therapeutic agents (e.g. small molecule drugs, nucleic acids and antibodies) to selectively target CSCs have been screened or proposed in recent years. Drug delivery technology-based approaches hold great potential for tackling the limitations impeding clinical applications of CSC-specific agents, such as poor water solubility, short circulation time and inconsistent stability. Properly designed nanocarrier-based therapeutic agents (or nanomedicines) offer new

possibilities of penetrating CSC niches and significantly increasing therapeutic drug accumulation in CSCs, which are difficult for free drug counterparts. In addition, intelligent nanomedicine holds great promise to overcome pump-mediated multidrug resistance which is driven by ATP and to decrease detrimental effects on normal somatic stem cells. In this review, we summarise the distinctive biological processes related to CSCs to highlight strategies against inherently drug-resistant CSCs. We then focus on some representative examples that give a glimpse into state-of-the-art nanomedicine approaches developed for CSCs elimination. A perspective on innovative therapeutic strategies and the potential direction of nanomedicine-based CSC therapy in the near future is also presented.

Shetty, A. K. and M. A. Winter (2012). "Immunization of children receiving immunosuppressive therapy for cancer or hematopoietic stem cell transplantation." Ochsner J **12**(3): 228-243.

In the past 3 decades, the number of immunocompromised children has increased steadily because of dramatic improvement in survival rates in certain malignancies as a result of intensive curative treatment regimens and an increase in the number of children undergoing life-saving hematopoietic stem cell transplantation (HSCT). Children receiving immunosuppressive therapy for cancer, as well as HSCT recipients, will benefit from vaccination but warrant close evaluation for a variety of reasons, such as the risk of developing severe infections, serious adverse events following certain vaccines, and decreased vaccine efficacy caused by poor immune response to vaccination. Various professional organizations have published vaccination guidelines for immunocompromised patients. Given their heterogeneity, recommendations for the immunization of immunocompromised patients may not be universally applicable. The safety of many commonly used vaccines has not been established in immunocompromised children. In addition, no large-scale vaccine studies have evaluated the clinical outcome of disease prevention in this population. All killed vaccines are generally safe, while live vaccines may be administered to immunocompromised children in select circumstances, depending on the degree of altered immunocompetence and the underlying primary condition. Healthcare providers should be knowledgeable about the indications, contraindications, and precautions for vaccine administration in immunocompromised patients. To protect immunocompromised patients, all family, household contacts, and healthcare workers should also be immunized with all routinely recommended vaccines. Pediatricians play a crucial role in identifying and effectively communicating the risks and benefits of vaccines to immunocompromised patients and their parents.

Shigdar, S., et al. (2012). "Cancer stem cell targeting: the next generation of cancer therapy and molecular imaging." Ther Deliv **3**(2): 227-244.

Cancer stem cells (CSCs) have the capacity to generate the heterogeneous lineages of all cancer cells comprising a tumor and these populations of cells are likely to be more relevant in determining prognosis. However, these cells do not operate in isolation, but instead rely upon signals co-opted from their microenvironment, making the targeting and imaging of CSCs within a cancer mass a daunting task. A better understanding of the molecular cell biology underlying CSC pathology will facilitate the development of new therapeutic targets and novel strategies for the successful eradication of cancer. In addition, the continued investigation of sensitive molecular-imaging modalities will enable more accurate staging, treatment planning and the ability to monitor the effectiveness of CSC-targeted therapies in vivo. In this review, we explore the possibilities and limitations of CSC-directed therapies and molecular imaging modalities.

Shukla, V., et al. (2018). "Identification of Novel Targets for Lung Cancer Therapy Using an Induced Pluripotent Stem Cell Model." Ann Am Thorac Soc **15**(Supplement_2): S127-S128.

RATIONALE: Despite extensive studies, the genetic and epigenetic mechanisms that mediate initiation and progression of lung cancers have not been fully elucidated. Previously, we have demonstrated that via complementary mechanisms, including DNA methylation, polycomb repressive complexes, and noncoding RNAs, cigarette smoke induces stem-like phenotypes that coincide with progression to malignancy in normal respiratory epithelia as well as enhanced growth and metastatic potential of lung cancer cells. OBJECTIVES: To further investigate epigenetic mechanisms contributing to stemness/pluripotency in lung cancers and potentially identify novel therapeutic targets in these malignancies, induced pluripotent stem cells were generated from normal human small airway epithelial cells. METHODS: Lung induced pluripotent stem cells were generated by lentiviral transduction of small airway epithelial cells of OSKM (Yamanaka) factors (octamer-binding transcription factor 4 [Oct4], sex-determining region Y box 2 [SOX2], Kruppel-like factor 4 [KLF4], and MYC proto-oncogene, bHLH transcription factor [MYC]). Western blot, real-time polymerase chain reaction, and chromatin

immunoprecipitation sequencing analysis were performed. RESULTS: The lung induced pluripotent stem cells exhibited hallmarks of pluripotency, including morphology, surface antigen and stem cell gene expression, in vitro proliferation, and teratoma formation. In addition, lung induced pluripotent stem cells exhibited no chromosomal aberrations, complete silencing of reprogramming transgenes, genomic hypermethylation, upregulation of genes encoding components of polycomb repressive complex 2, hypermethylation of stem cell polycomb targets, and modulation of more than 15,000 other genes relative to parental small airway epithelial cells. Additional sex combs like-3 (ASXL3), encoding a polycomb repressive complex 2-associated protein not previously described in reprogrammed cells, was markedly upregulated in lung induced pluripotent stem cell as well as human small cell lung cancer lines and specimens. Overexpression of the additional sex combs like-3 gene correlated with increased genomic copy number in small cell lung cancer lines. Knock-down of the additional sex combs like-3 gene inhibited proliferation, clonogenicity, and teratoma formation by lung induced pluripotent stem cells and significantly diminished in vitro clonogenicity and growth of small cell lung cancer cells in vivo. CONCLUSIONS: Collectively, these studies highlight the potential utility of this lung induced pluripotent stem cell model for elucidating epigenetic mechanisms contributing to pulmonary carcinogenesis and suggest that additional sex combs like-3 is a novel target for small cell lung cancer therapy.

Silva, L. C., et al. (2015). "The Impact of Low-Level Laser Therapy on Oral Mucositis and Quality of Life in Patients Undergoing Hematopoietic Stem Cell Transplantation Using the Oral Health Impact Profile and the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation Questionnaires." Photomed Laser Surg **33**(7): 357-363.

OBJECTIVE: The aim of this study was to assess the impact of low-level laser therapy (LLLT) on oral mucositis (OM) and quality of life (QoL) of hematopoietic stem cell transplantation (HSCT) patients. BACKGROUND DATA: OM related to high-dose chemotherapy is often associated with increased risk of mortality and impaired QoL in HSCT patients. LLLT has shown promising effects in the prevention and treatment of chemotherapy-induced OM. There is a dearth of literature focused on subjective aspects involving OM and QoL in patients receiving LLLT. METHODS: Thirty-nine patients were randomly assigned to two groups: control (n=19) and laser (n=20). LLLT was performed from the 1st day of the conditioning regimen until day 7 post-HSCT (D+7). OM severity was evaluated in all patients [World Health Organization (WHO) scale]. A blinded observer collected subjective outcomes from patients on admission (AD), D+7 and at discharge (DC). QoL was assessed using the Oral Health Impact Profile (OHIP-14) and the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT) questionnaires. Statistical analyses included descriptive, bivariate and multivariate (generalized estimating equation) tests. RESULTS: The overall FACT-BMT ($p=0.074$) and OHIP-14 ($p=0.749$) scores were not associated with the use of laser therapy. Both instruments showed a deterioration in QoL for the whole sample on D+7. The laser group presented less severe OM than the control group ($p<0.001$). CONCLUSIONS: LLLT did not influence the oral and general health-related QoL of patients undergoing HSCT, although it was clinically effective in reducing the severity of chemotherapy-induced OM.

Sisay, M., et al. (2017). "The RANK/RANKL/OPG system in tumorigenesis and metastasis of cancer stem cell: potential targets for anticancer therapy." Onco Targets Ther **10**: 3801-3810.

The molecular triad involving receptor activator of nuclear factor kbeta (RANK)/RANK ligand (RANKL)/osteoprotegerin cytokine system has been well implicated in several physiological and pathological processes including bone metabolism, mammary gland development, regulation of the immune function, tumorigenesis and metastasis of cancer stem cell, thermoregulation, and vascular calcification. However, this review aimed to summarize several original and up-to-date articles focusing on the role of this signaling system in cancer cell development and metastasis as well as potential therapeutic agents targeting any of the three tumor necrotic factor super family proteins and/or their downstream signaling pathways. The RANK/RANKL axis has direct effects on tumor cell development. The system is well involved in the development of several primary and secondary tumors including breast cancer, prostate cancer, bone tumors, and leukemia. The signaling of this triad system has also been linked to tumor invasiveness in the advanced stage. Bone is by far the most common site of cancer metastasis. Several therapeutic agents targeting this system have been developed. Among them, a monoclonal antibody, denosumab, was clinically approved for the treatment of osteoporosis and cancer-related diseases.

Smeland, K. B., et al. (2016). "A national study on conditional survival, excess mortality and second cancer after high dose therapy with autologous stem cell transplantation for non-Hodgkin lymphoma." Br J Haematol **173**(3): 432-443.

This national population-based study aimed to investigate conditional survival and standardized mortality ratios (SMR) after high-dose therapy with autologous stem-cell transplantation (HDT-ASCT) for non-Hodgkin lymphoma (NHL), and to analyse cause of death, relapses and second malignancies. All patients >/=18 years treated with HDT-ASCT for NHL in Norway between 1987 and 2008 were included (n = 578). Information from the Cause of Death Registry and Cancer Registry of Norway were linked with clinical data. The 5-, 10- and 20-year overall survival was 61% (95% confidence interval [CI] 56-64%), 52% (95%CI 48-56%) and 45% (95%CI 40-50%), respectively. The 5-year survival conditional on having survived 2, 5 and 10 years after HDT-ASCT was 81%, 86% and 93%. SMRs were 12.3 (95%CI 11.0-13.9), 4.9 (95%CI 4.1-5.9), 2.4 (95%CI 1.8-3.2) and 1.0 (95%CI 0.6-1.8) for the entire cohort and for patients having survived 2, 5 and 10 years after HDT-ASCT respectively. Of the 281 deaths observed, 77% were relapse-related. Treatment-related mortality was 3.6%. The 10-year cumulative incidence of second malignancies was 7.9% and standardized incidence ratio was 2.0 (95%CI 1.5-2.6). NHL patients treated with HDT-ASCT were at increased risk of second cancer and premature death. The mortality was still elevated at 5 years, but after 10 years mortality equalled that of the general population.

Smith, B. H., et al. (2018). "Clinical laboratory and imaging evidence for effectiveness of agarose-agarose macrobeads containing stem-like cells derived from a mouse renal adenocarcinoma cell population (RMBs) in treatment-resistant, advanced metastatic colorectal cancer: Evaluation of a biological-systems approach to cancer therapy (U.S. FDA IND-BB 10091; NCT 02046174, NCT 01053013)." Chin J Cancer Res **30**(1): 72-83.

Objective: The complexity, heterogeneity and capacity of malignant neoplastic cells and tumors for rapid change and evolution suggest that living-cell-based biological-systems approaches to cancer treatment are merited. Testing this hypothesis, the tumor marker, metabolic activity, and overall survival (OS) responses, to the use of one such system, implantable macrobeads [RENCA macrobeads (RMBs)], in phase I and IIa clinical trials in advanced, treatment-resistant metastatic colorectal cancer (mCRC) are described here. Methods: Forty-eight mCRC patients (30 females; 18 males), who had failed all available, approved treatments, underwent RMB implantation (8 RMB/kg body weight) up to 4 times in phase I and phase IIa open-label trials. Physicals, labs [tumor and inflammation markers, lactate dehydrogenase (LDH)] and positron emission tomography-computed tomography (PET-CT) imaging to measure number/volume and metabolic activity of the tumors were performed pre- and 3-month-post-implantation to evaluate safety and initial efficacy (as defined by biological responses). PET-CT maximum standard uptake value (SUVmax) (baseline and d 90; SUVmax >/=2.5), LDH, and carcinoembryonic antigen (CEA) and/or cancer antigen 19-9 (CA 19-9) response (baseline, d 30 and/or d 60) were assessed and compared to OS. Results: Responses after implantation were characterized by an at least 20% decrease in CEA and/or CA 19-9 in 75% of patients. Fluorodeoxyglucose (FDG)-positive lesions (phase I, 39; 2a, 82) were detected in 37/48 evaluable patients, with 35% stable volume and stable or decreased SUV (10) plus four with necrosis; 10, increased tumor volume, SUV. LDH levels remained stable and low in Responders (R) (d 0-60, 290.4-333.9), but increased steadily in Non-responders (NR) (d 0-60, 382.8-1,278.5) (d 60, P=0.050). Responders to RMBs, indicated by the changes in the above markers, correlated with OS (R mean OS=10.76 months; NR mean OS=4.9 months; P=0.0006). Conclusions: The correlations of the tumor marker, tumor volume and SUV changes on PET-CT, and LDH levels themselves, and with OS, support the concept of a biological response to RMB implantation and the validity of the biological-systems approach to mCRC. A phase III clinical trial is planned.

Stack, J. P., et al. (2018). "Cancer therapy-induced cardiomyopathy: can human induced pluripotent stem cell modelling help prevent it?" Eur Heart J.

Cardiotoxic effects from cancer therapy are a major cause of morbidity during cancer treatment. Unexpected toxicity can occur during treatment and/or after completion of therapy, into the time of cancer survivorship. While older drugs such as anthracyclines have well-known cardiotoxic effects, newer drugs such as tyrosine kinase inhibitors, proteasome inhibitors, and immunotherapies also can cause diverse cardiovascular and metabolic complications. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) are increasingly being used as instruments for disease modelling, drug discovery, and mechanistic toxicity studies. Promising results with hiPSC-CM chemotherapy studies are raising hopes for improving cancer therapies through personalized medicine and safer drug development. Here, we review the cardiotoxicity profiles of common chemotherapeutic agents as well as efforts to model them in vitro using hiPSC-CMs.

Sun, T. M., et al. (2014). "Cancer stem cell therapy using doxorubicin conjugated to gold

nanoparticles via hydrazone bonds." Biomaterials **35**(2): 836-845.

Nanoparticle-mediated delivery of chemotherapies has demonstrated enhanced anti-cancer efficacy, mainly through the mechanisms of both passive and active targeting. Herein, we report other than these well-elucidated mechanisms, rationally designed nanoparticles can efficiently deliver drugs to cancer stem cells (CSCs), which in turn contributes significantly to the improved anti-cancer efficacy. We demonstrate that doxorubicin-tethered gold nanoparticles via a poly (ethylene glycol) spacer and an acid-labile hydrazone bond mediate potent doxorubicin delivery to breast CSCs, which reduces their mammosphere formation capacity and their cancer initiation activity, eliciting marked enhancement in tumor growth inhibition in murine models. The drug delivery mediated by the nanoparticles also markedly attenuates tumor growth during off-therapy stage by reducing breast CSCs in tumors, while the therapy with doxorubicin alone conversely evokes an enrichment of breast CSCs. Our findings suggest that with well-designed drug delivery system, the conventional chemotherapeutic agents are promising for cancer stem cell therapy.

Sun, X. Y., et al. (2011). "Mesenchymal stem cell-mediated cancer therapy: A dual-targeted strategy of personalized medicine." World J Stem Cells **3**(11): 96-103.

Cancer remains one of the leading causes of mortality and morbidity throughout the world. To a significant extent, current conventional cancer therapies are symptomatic and passive in nature. The major obstacle to the development of effective cancer therapy is believed to be the absence of sufficient specificity. Since the discovery of the tumor-oriented homing capacity of mesenchymal stem cells (MSCs), the application of specific anticancer gene-engineered MSCs has held great potential for cancer therapies. The dual-targeted strategy is based on MSCs' capacity of tumor-directed migration and incorporation and in situ expression of tumor-specific anticancer genes. With the aim of translating bench work into meaningful clinical applications, we describe the tumor tropism of MSCs and their use as therapeutic vehicles, the dual-targeted anticancer potential of engineered MSCs and a putative personalized strategy with anticancer gene-engineered MSCs.

Tabassum, N., et al. (2018). "Nanomedicine in cancer stem cell therapy: from fringe to forefront." Cell Tissue Res.

Nanomedicine is the spin-off of modern medicine and nanotechnology and aims to prevent and treat diseases using nanoscale materials such as biocompatible nanoparticles and nanorobots. Targeted cellular and tissue-specific clinical applications with maximal therapeutic effects and insignificant side effects could be achieved by the pursuit of nanotechnology in medicine and healthcare regimen. The majority of conventional cancer therapies eliminate the cells of the tumor but not the cancer stem cells (CSCs). Conversely, the use of nanotechnology in CSC-based therapies is an emerging field of biomedical sciences. This article summarizes the recent trends and application of nanomedicine especially in CSC therapy along with its limitations.

Tampakis, A., et al. (2017). "Nestin and CD146 expression in metaplastic breast cancer: stem-cell therapy in need? Lessons reported from a male patient." Eur Rev Med Pharmacol Sci **21**(18): 4137-4140.

OBJECTIVE: Metaplastic breast carcinomas represent a rare subtype of breast cancer exhibiting aggressive clinical features. They appear as highly chemoresistant tumors, therefore showing poor outcome and high rates of local recurrence or distant metastasis. CASE REPORT: A 37-year-old greek man was referred to our hospital for evaluation of a locally advanced, ulcerated, fixed, irregular and hard in consistency mass covering his left breast and chest wall. Further work out with CT and biopsy of the tumor revealed a triple negative metaplastic breast cancer classified as cT4cN3cM1. The patient received first line chemotherapy and afterward a palliative resection of the tumor. The histology revealed the presence of a combined triple negative adenocarcinoma with a predominant metaplastic squamous carcinoma and a spindle cell (sarcomatoid) carcinoma of the breast. In the tissue sample stem cell markers, nestin and CD146 (MCAM) were expressed, enhancing the theory that cancer cells of this tumor could possibly harbor stem cell properties. The patient received several chemotherapy regimens but died 6 months after the initiation of treatment. CONCLUSIONS: Metaplastic breast cancer consists of cells with stem cell properties. New targeted therapies are warranted in the view of the tumor's high resistance to conventional chemotherapy. Targeting nestin and CD146 might be a promising therapy as they seem to be implicated in the EMT pathway.

Tang, C., et al. (2007). "Cancer stem cell: target for anti-cancer therapy." FASEB J **21**(14): 3777-3785.

Cancer has long been viewed as a heterogeneous population of cells. While the great majority of cells that make up tumors are destined to differentiate, albeit aberrantly, and eventually stop dividing, only a minority population of cells, termed cancer stem cells, possess extensive self-renewal capability and can

recapitulate tumor pathophysiology in an immune-compromised animal model. Tumor-initiating cells have been identified and isolated in a variety of cancers of the blood, breast, central nervous system, pancreas, skin, head and neck, colon, and prostate. In this review we present scientific evidence supporting the cancer stem cell model of tumor progression, and discuss the experimental and therapeutic implications. The concept of cancer stem cells may have profound implications for our understanding of tumor biology and for the design of novel treatments targeted toward these cells. Current therapeutic strategies include targeting the cancer stem cell as well as its microenvironmental niche. We present an interesting, novel strategy that takes into account the reactive oxygen species status in cancer stem cells and how it might serve as a method for eradicating these cells in tumor growth.

Todorova, R. (2014). "Ewing's sarcoma cancer stem cell targeted therapy." Curr Stem Cell Res Ther **9**(1): 46-62.

Ewing`s sarcoma (ES) family of tumors (ESFTs) are round cell tumors of bone and soft tissues, afflicting children and young adults. This review summarizes the present findings about ES cancer stem cell (CSC) targeted therapy: prognostic factors, chromosomal translocations, initiation, epigenetic mechanisms, candidate cell of ES origin (Mesenchymal stem cells (MSCs) and Neural crest stem cells (NCSCs)). The ES CSC model, histopathogenesis, histogenesis, pathogenesis, ES mediated Hematopoietic stem progenitor cells (HSPCs) senescence are also discussed. ESFTs therapy is reviewed concerning CSCs, radiotherapy, risk of subsequent neoplasms, stem cell (SC) support, promising therapeutic targets for ES CSCs (CSC markers, immune targeting, RNAi phenotyping screens, proposed new drugs), candidate EWS-FLI1 target genes and further directions (including human embryonic stem cells (hESCs)). Bone marrow-derived human MSCs are permissive for EWS-FLI1 expression with transition to ESFT-like cellular phenotype. ESFTs are genetically related to NCSC, permissive for EWS-FLI1 expression and susceptible to oncogene-induced immortalization. Primitive neuroectodermal features and MSC origin of ESFTs provide a basis of immune targeting. The microRNAs profile of ES CSCs is shared by ESCs and CSCs from divergent tumor types. Successful reprogramming of differentiated human somatic cells into a pluripotent state allows creation of patient- and disease-specific SCs. The functional role of endogenous EWS at stem cell level on both senescence and tumorigenesis is a link between cancer and aging. The regulatory mechanisms of oncogenic activity of EWS fusions could provide new prognostic biomarkers, therapeutic opportunities and tumor-specific anticancer agents against ESFTs.

Torigoe, T., et al. (2013). "Constitutive expression and activation of stress response genes in cancer stem-like cells/tumour initiating cells: potent targets for cancer stem cell therapy." Int J Hyperthermia **29**(5): 436-441.

Cancer stem-like cells (CSCs)/tumour-initiating cells (TICs) are defined as the small population of cancer cells that have stem cell-like phenotypes and high capacity for tumour initiation. These cells may have a huge impact in the field of cancer therapy since they are extremely resistant to standard chemoradiotherapy and thus are likely to be responsible for disease recurrence after therapy. Therefore, extensive efforts are being made to elucidate the pathological and molecular properties of CSCs/TICs and, with this information, to establish efficient anti-CSC/TIC targeting therapies. This review considers recent findings on stress response genes that are preferentially expressed in CSCs/TICs and their roles in tumour-promoting properties. Implications for a novel therapeutic strategy targeting CSCs/TICs are also discussed.

Tosoni, D., et al. (2017). "Pre-clinical validation of a selective anti-cancer stem cell therapy for Numb-deficient human breast cancers." EMBO Mol Med **9**(5): 655-671.

The cell fate determinant Numb is frequently downregulated in human breast cancers (BCs), resulting in p53 inactivation and an aggressive disease course. In the mouse mammary gland, Numb/p53 downregulation leads to aberrant tissue morphogenesis, expansion of the stem cell compartment, and emergence of cancer stem cells (CSCs). Strikingly, CSC phenotypes in a Numb-knockout mouse model can be reverted by Numb/p53 restoration. Thus, targeting Numb/p53 dysfunction in Numb-deficient human BCs could represent a novel anti-CSC therapy. Here, using patient-derived xenografts, we show that expansion of the CSC pool, due to altered self-renewing divisions, is also a feature of Numb-deficient human BCs. In these cancers, using the inhibitor Nutlin-3 to restore p53, we corrected the defective self-renewal properties of Numb-deficient CSCs and inhibited CSC expansion, with a marked effect on tumorigenicity and metastasis. Remarkably, a regimen combining Nutlin-3 and chemotherapy induced persistent tumor growth inhibition, or even regression, and prevented CSC-driven tumor relapse after removal of chemotherapy. Our data provide a pre-clinical proof-of-concept that targeting Numb/p53 results in a specific anti-CSC therapy in human BCs.

Tsujii, M. (2014). "[Cancer therapy targeting cancer stem cell]." Nihon Rinsho **72**(1): 35-41.

Cancer stem cells (CSCs) represent a subpopulation of tumour cells endowed with self-renewal and multi-lineage differentiation capacity. Clinically, drug resistance is the most important feature, because CSCs resist conventional cancer therapies and are involved in relapse. Therefore, major clinical challenges towards the complete eradication of minimal residual cancer are likely to target CSCs. Several molecules have been investigated as a target: specific signal transduction, cell surface marker, and microenviromental factors. Several drugs (salinomycin, metformin) have been also identified by chemical screening. For clinical use, however, more precise molecular mechanisms remain to be clarified.

Ueda, Y., et al. (2004). "Mobilization of peripheral blood stem cells (PBSCs) after etoposide, adriamycin and cisplatin therapy, and a multimodal cell therapy approach with PBSCs in advanced gastric cancer." Oncol Rep **12**(2): 323-332.

The EAP combination of etoposide (ETP), doxorubicin (ADM) and cisplatin (CDDP) has been reported to be highly active for advanced gastric cancer. However, it is associated with severe myelotoxicity, and its use has declined. We examined whether peripheral blood stem cells (PBSCs) could be mobilized during hematopoietic recovery after EAP, and assessed the possibility of using multimodal cell therapy with PBSCs for the treatment of advanced gastric cancer. Five men with advanced gastric adenocarcinoma were enrolled. All patients were chemotherapy-naive. EAP (ETP, 360 mg/m2; ADM, 40 mg/m2; CDDP, 80 mg/m2) was given to each patient, and myelotoxicity was carefully monitored. Granulocyte colony-stimulating factor was administered after the neutrophil nadir, and PBSCs were collected by leukapheresis during hematopoietic recovery. The median nadir of the neutrophil count after EAP was 225/ml, occurring between day 17 and 20. Sufficient numbers of PBSCs [CD34(+) cells, CFU-GM] could be mobilized in 4/5 patients. A 45-year-old patient with extended lymph node metastasis received high-dose EAP with peripheral blood stem cell transplantation (PBSCT), followed by cancer vaccine therapy with dendritic cells (DCs), induced from cryopreserved PBSCs. Both high-dose EAP with PBSCT and DC-based immunotherapy was safely performed for the first time against gastric cancer. Although associated with severe myelotoxicity, EAP can mobilize sufficient numbers of PBSCs during hematopoietic recovery. Multimodal cell therapy combining high-dose chemotherapy with PBSCT and DC-based immunotherapy is feasible and can be a reasonable approach in advanced gastric cancer.

Ursula, A., et al. (2018). "Prodrug suicide gene therapy for cancer targeted intracellular by mesenchymal stem cell exosomes." Int J Cancer.

The natural behavior of mesenchymal stem cells (MSCs) and their exosomes in targeting tumors is a promising approach for curative therapy. Human tumor tropic mesenchymal stem cells (MSCs) isolated from various tissues and MSCs engineered to express the yeast cytosine deaminase::uracil phosphoribosyl transferase suicide fusion gene (yCD::UPRT-MSCs) released exosomes in conditional medium (CM). Exosomes from all tissue specific yCD::UPRT-MSCs contained mRNA of the suicide gene in the exosome's cargo. When the CM was applied to tumor cells, the exosomes were internalized by recipient tumor cells and in the presence of the prodrug 5-fluorocytosine (5-FC) effectively triggered dose-dependent tumor cell death by endocytosed exosomes via an intracellular conversion of the prodrug 5-FC to 5-fluorouracil. Exosomes were found to be responsible for the tumor inhibitory activity. The presence of microRNAs in exosomes produced from naive MSCs and from suicide gene transduced MSCs did not differ significantly. MicroRNAs from yCD::UPRT-MSCs were not associated with therapeutic effect. MSC suicide gene exosomes represent a new class of tumor cell targeting drug acting intracellular with curative potential.

van der Wall, E., et al. (1995). "High-dose carboplatin, thiotepa and cyclophosphamide (CTC) with peripheral blood stem cell support in the adjuvant therapy of high-risk breast cancer: a practical approach." Br J Cancer **71**(4): 857-862.

In 29 chemotherapy-naive patients with stage II-III breast cancer, peripheral blood stem cells (PBSCs) were mobilised following fluorouracil 500 mg m-2, epirubicin 90-120 mg m-2 and cyclophosphamide 500 mg m-2 (FEC) and granulocyte colony-stimulating factor (G-CSF; Filgrastim) 300 microgram s.c. daily. In all but one patient, mobilisation was successful, requiring three or fewer leucocytopheresis sessions in 26 patients; 28 patients subsequently underwent high-dose chemotherapy consisting of carboplatin 1600 mg m-2, thiotepa 480 mg m-2 and cyclophosphamide 6 g m-2 (CTC) followed by PBSC transplantation. Haemopoietic engraftment was rapid with a median time to neutrophils of 500 x 10(6) l (-1) of 9 days (range 8-10) in patients who received G-CSF after PBSC-transplantation; platelet transfusion independence was reached within a median of 10 days (range 7-16). Neutropenic fever occurred in 96% of patients. Gastrointestinal toxicity was substantial but

reversible. Renal, neural or ototoxicity was not observed. Complications related to the central venous catheter were encountered in 64% of patients, with major vein thrombosis occurring in 18%. High-dose CTC-chemotherapy with PBSC-transplantation, harvested after mobilisation with FEC and G-CSF, is reasonably well tolerated without life-threatening toxicity and is a suitable high-dose strategy for the adjuvant treatment of breast cancer.

Vicente-Duenas, C., et al. (2015). "Tumoral stem cell reprogramming as a driver of cancer: Theory, biological models, implications in cancer therapy." Semin Cancer Biol **32**: 3-9.

Cancer is a clonal malignant disease originated in a single cell and characterized by the accumulation of partially differentiated cells that are phenotypically reminiscent of normal stages of differentiation. According to current models, therapeutic strategies that block oncogene activity are likely to selectively target tumor cells. However, recent evidences have revealed that cancer stem cells could arise through a tumor stem cell reprogramming mechanism, suggesting that genetic lesions that initiate the cancer process might be dispensable for tumor progression and maintenance. This review addresses the impact of these results toward a better understanding of cancer development and proposes new approaches to treat cancer in the future.

Vlashi, E. and F. Pajonk (2015). "Cancer stem cells, cancer cell plasticity and radiation therapy." Semin Cancer Biol **31**: 28-35.

Since the first prospective identification of cancer stem cells in solid cancers the cancer stem cell hypothesis has reemerged as a research topic of increasing interest. It postulates that solid cancers are organized hierarchically with a small number of cancer stem cells driving tumor growth, repopulation after injury and metastasis. They give rise to differentiated progeny, which lack these features. The model predicts that for any therapy to provide cure, all cancer stem cells have to be eliminated while the survival of differentiated progeny is less critical. In this review we discuss recent reports challenging the idea of a unidirectional differentiation of cancer cells. These reports provide evidence supporting the idea that non-stem cancer cells exhibit a remarkable degree of plasticity that allows them to re-acquire cancer stem cell traits, especially in the context of radiation therapy. We summarize conditions under which differentiation is reversed and discuss the current knowledge of the underlying mechanisms.

Wadosky, K. M., et al. (2017). "Evasion of targeted cancer therapy through stem-cell-like reprogramming." Mol Cell Oncol **4**(2): e1291397.

Prostate cancer variants expressing alternative lineage markers appear at relapse from antiandrogen therapy. We show that loss of the retinoblastoma (RB1) and tumor protein 53 (TP53) genes drives expression of stem cell reprogramming factors, lineage plasticity, and antiandrogen resistance. Epigenetic manipulation restores antiandrogen sensitivity-suggesting an approach for treating lethal prostate cancers.

Wang, J., et al. (2012). "High-dose chemotherapy followed by autologous stem cell transplantation as a first-line therapy for high-risk primary breast cancer: a meta-analysis." PLoS One **7**(3): e33388.

BACKGROUND AND OBJECTIVES: Several trials have generated conflicting results about the results of high-dose chemotherapy followed by autologous stem cell transplantation (HDCT) for primary breast cancer. This meta-analysis summarizes the available evidence from all suitable studies. DESIGN AND METHODS: Prospective, randomized trials with HDCT as a first-line therapy for primary breast cancer were included in this meta-analysis. The primary outcome of interest for our analysis was survival (disease-free survival and overall survival); secondary endpoints included treatment-related mortality (TRM) and second (non-breast) cancers. We used a median age of 47, a PR positive rate of 50% and a premenopausal rate of 70% as cutoff values to complete the subgroup analyses, which were pre-planned according to the prepared protocol. RESULTS: Fourteen trials with 5747 patients were eligible for the meta-analysis. Compared with non-HDCT, non-significant second (non-breast) cancers (RR = 1.28; 95% CI = 0.82-1.98) and higher TRM (RR = 3.42; 95% CI = 1.32-8.86) were associated with HDCT for primary breast cancer. A significant DFS benefit of HDCT was documented (HR = 0.89; 95% CI = 0.79-0.99). No difference in OS (overall survival) was found when the studies were pooled (HR = 0.91; 95% CI = 0.82-1.00, p = 0.062). In subgroup analysis, age and hormone receptor status had a significant interaction with prolonged DFS and OS. CONCLUSIONS: HDCT has a benefit on DFS and OS compared to SDC in some special patients with high-risk primary breast cancer.

Wang, T., et al. (2015). "Cancer stem cell targeted therapy: progress amid controversies." Oncotarget **6**(42): 44191-44206.

Although cancer stem cells have been well characterized in numerous malignancies, the fundamental characteristics of this group of cells, however, have been challenged by some recent observations: cancer stem cells may not necessary to

be rare within tumors; cancer stem cells and non-cancer stem cells may undergo reversible phenotypic changes; and the cancer stem cells phenotype can vary substantially between patients. Here the current status and progresses of cancer stem cells theory is illustrated and via providing a panoramic view of cancer therapy, we addressed the recent controversies regarding the feasibility of cancer stem cells targeted anti-cancer therapy.

Wei, P., et al. (2014). "Cancer stem-like cell: a novel target for nasopharyngeal carcinoma therapy." Stem Cell Res Ther **5**(2): 44.

Nasopharyngeal carcinoma (NPC) is the most common cancer originating in the nasopharynx, and is extremely common in southern regions of China. Although the standard combination of radiotherapy and chemotherapy has improved the efficiency in patients with NPC, relapse and early metastasis are still the common causes of mortality. Cancer stem-like cells (CSCs) or tumor initial cells are hypothesized to be involved in cancer metastasis and recurrence. Over the past decade, increasing numbers of studies have been carried out to identify CSCs from human NPC cells and tissues. The present paper will summarize the investigations on nasopharyngeal CSCs, including isolation, characteristics, and therapeutic approaches. Although there are still numerous challenges to translate basic research into clinical applications, understanding the molecular details of CSCs is essential for developing effective strategies to prevent the recurrence and metastasis of NPC.

Williams, S. F., et al. (1992). "High-dose consolidation therapy with autologous stem-cell rescue in stage IV breast cancer: follow-up report." J Clin Oncol **10**(11): 1743-1747.

PURPOSE: Fifty-nine patients with newly diagnosed metastatic breast cancer were treated with induction chemotherapy followed by high-dose intensification and autologous stem-cell rescue (ASCR) to determine therapeutic efficacy. PATIENTS AND METHODS: Induction consisted of cyclophosphamide, doxorubicin, vincristine, and methotrexate with leucovorin rescue (LOMAC) in 27 patients, or fluorouracil, cisplatin, doxorubicin, and cyclophosphamide (FCAP) in 32 patients. Intensification after LOMAC was cyclophosphamide and thiotepa (CyTepa) with ASCR, and after FCAP it was cyclophosphamide, thiotepa, and carmustine (BCNU) in all but eight patients who received CyTepa. RESULTS: Median survival from study entry for the entire group was 13.3 months. Median time to progression from reinfusion for the 45 patients who underwent intensification was 7.5 months. After LOMAC and intensification, there were 12 complete responses (CR) (nine partial responses [PRs] after induction converted to CRs). Responses after FCAP and intensification were eight CRs (two PRs after induction converted to CRs). Median time to treatment failure from reinfusion was 5.4 months for LOMAC and intensification, and was 10.5 months for FCAP and intensification. Median survival from study entry was 15.1 months for all 27 LOMAC patients and 9.3 months for all 32 FCAP patients. Median time to treatment failure from reinfusion for 11 patients who were CRs at intensification has not been reached and is more than 13 months compared with a median of 5.5 months for the 23 patients in partial remission at intensification. CONCLUSIONS: High-dose intensification therapy has led to increased CR rates in metastatic breast cancer. The role of such therapy in the treatment of stage IV breast cancer requires further refinement.

Williams, S. F., et al. (1989). "High-dose consolidation therapy with autologous stem cell rescue in stage IV breast cancer." J Clin Oncol **7**(12): 1824-1830.

We designed a phase II study to determine whether induction chemotherapy (CT) consisting of leucovorin, vincristine, methotrexate, doxorubicin, and cyclophosphamide (LOMAC) followed by high-dose intensification chemotherapy (ICT) with cyclophosphamide, thiotepa, and autologous stem cell rescue (ASCR) could increase the complete response (CR) rate and survival in women with stage IV breast cancer. Twenty-nine women were enrolled on study; 16 patients had received prior adjuvant chemotherapy and no patient had received chemotherapy for stage IV disease. Two patients were found to be ineligible and excluded from further analysis. Of the 27 patients treated, four (15%) obtained a CR and 15 (56%) a partial response (PR) after LOMAC induction, for an overall response rate of 70%. Of the 22 patients treated with ICT, 12 patients had a CR, and nine were in PR after induction and converted to CR after ICT. The toxicities included nausea/vomiting, mucositis, diarrhea, dermatitis, alopecia, and infections secondary to neutropenia. The 1-year survival is 60%; the median has not yet been reached. The time to treatment failure for patients on study is 10 months. The treatment approach of ICT and ASCR following induction chemotherapy can lead to an improved CR rate in stage IV breast cancer. How this increased CR rate leads to a prolonged disease-free survival requires further follow-up.

Wolfe, A. R. and W. A. Woodward (2015). "Breast Cancer Stem Cell Correlates as Predicative Factors for Radiation Therapy." Semin Radiat Oncol **25**(4): 251-259.

In today's era of personalized medicine, the use of radiation therapy for breast cancer is still tailored to the type of surgery and the stage of the cancer. The future of breast radiation oncology would hopefully entail selecting patients for whom there is a clear benefit for the use of radiation therapy. To get to this point we need reliable predictors of radiation response. Cancer stem cells have been correlated to radiation resistance and outcome for patients with breast cancer, and there is considerable interest in whether cancer stem cell markers or biologic surrogates may be predictive of response to radiation therapy. We review the data or in some cases lack of data regarding stem cell correlates as predictors of radiation resistance as well as the correlation of known predictors with stem cell biology. More research is certainly needed to investigate potential predictors of radiation response, stem cell or otherwise, to move us toward the goal of personalized radiation therapy.

Wu, J., et al. (2016). "Synergistic Chemo-Photothermal Therapy of Breast Cancer by Mesenchymal Stem Cell-Encapsulated Yolk-Shell GNR@HPMO-PTX Nanospheres." ACS Appl Mater Interfaces **8**(28): 17927-17935.

Mesenchymal stem cells (MSCs) have attracted increasing attention as vehicles for cancer treatment. Herein, MSC-based synergistic oncotherapy strategy is presented for the first time. To achieve this goal, yolk-shell structured gold nanorod embedded hollow periodic mesoporous organosilica nanospheres (GNR@HPMOs) with high paclitaxel (PTX) loading capability and excellent photothermal transfer ability upon near-infrared (NIR) light irradiation are first prepared. Cytotoxicity and migration assays show that the viability and tumor-homing capability of MSCs are well-retained after internalization of high content of PTX loaded GNR@HPMOs (denoted as GNR@HPMOs-PTX). In vitro experiments show the GNR@HPMOs-PTX loaded MSCs (GNR@HPMOs-PTX@MSCs) possess synergistic chemo-photothermal killing effects for breast cancer cells. Also, photoacoustic imaging shows that the MSCs can improve dispersion and distribution in tumor tissue for GNR@HPMOs-PTX after intratumoral injection. In vivo experiments in breast cancer model of nude mice further demonstrate that the GNR@HPMOs-PTX@MSCs significantly inhibit tumor growth, suggesting their great potential for synergistic therapy of cancer.

Xu, L. (2013). "Cancer stem cell in the progression and therapy of pancreatic cancer." Front Biosci (Landmark Ed) **18**: 795-802.

Pancreatic cancer (PC) is an aggressive malignancy with a high incidence of distant metastasis and mortality. Emerging evidence has demonstrated that pancreatic cancer stem cells (CSCs), which have the potential to self-renew and are pluripotent, are crucially important in the progression and therapy of PC. The origin of pancreatic CSCs was suggested to be pancreatic acinar cells, centroacinar cells, or acinar-ductal metaplasia. And several CSC-specific markers for pancreatic cancer have been reported, including CD133, CD24, CD44 and CXCR4. Several studies reported the molecular mechanisms regulating human pancreatic CSCs characteristics. In the progression of PC, CSCs are linked with the aggressiveness of PC with association of epithelial to mesenchymal transition (EMT). In the therapy of PC, especially chemotherapy, CSCs offer new insight into PC therapy, especially the mechanism of drug resistance. Therefore, strategies for modulating and treating CSCs can lead to novel targeted therapies for pancreatic cancer.

Yang, J., et al. (2012). "Tumor tropism of intravenously injected human-induced pluripotent stem cell-derived neural stem cells and their gene therapy application in a metastatic breast cancer model." Stem Cells **30**(5): 1021-1029.

Human pluripotent stem cells can serve as an accessible and reliable source for the generation of functional human cells for medical therapies. In this study, we used a conventional lentiviral transduction method to derive human-induced pluripotent stem (iPS) cells from primary human fibroblasts and then generated neural stem cells (NSCs) from the iPS cells. Using a dual-color whole-body imaging technology, we demonstrated that after tail vein injection, these human NSCs displayed a robust migratory capacity outside the central nervous system in both immunodeficient and immunocompetent mice and homed in on established orthotopic 4T1 mouse mammary tumors. To investigate whether the iPS cell-derived NSCs can be used as a cellular delivery vehicle for cancer gene therapy, the cells were transduced with a baculoviral vector containing the herpes simplex virus thymidine kinase suicide gene and injected through tail vein into 4T1 tumor-bearing mice. The transduced NSCs were effective in inhibiting the growth of the orthotopic 4T1 breast tumor and the metastatic spread of the cancer cells in the presence of ganciclovir, leading to prolonged survival of the tumor-bearing mice. The use of iPS cell-derived NSCs for cancer gene therapy bypasses the sensitive ethical issue surrounding the use of cells derived from human fetal tissues or human embryonic stem cells. This approach may also help to overcome problems associated with allogeneic transplantation of other types of human NSCs.

Yen, C. H., et al. (2018). "Gynura divaricata attenuates tumor growth and tumor relapse after cisplatin therapy in HCC xenograft model through suppression of cancer stem cell growth and Wnt/beta-catenin signalling." J Ethnopharmacol **213**: 366-375.

ETHNOPHARMACOLOGICAL RELEVANCE: Gynura divaricata subsp. formosana is a widely used traditional herbal medicine for treating liver disorders such as hepatitis and liver cancer in Taiwan. AIM OF THE STUDY: This study was aimed to evaluate the anti-cancer and cancer stabilization effect of water extract of the aerial part of G. divaricata (GD extract) both in vitro and in vivo. MATERIALS AND METHODS: Cytotoxicity and anti-proliferative effects of GD extract alone and in combination with cisplatin were determined by alamarBlue and clonogenic assay. Cancer stem cell (CSC) inhibition and the expression of CSC markers were revealed by sphere formation assay and real-time PCR (qPCR). The in vivo anti-cancer effect of GD extract was evaluated in Huh7 xenograft mice model and Ki-67 expression were also measured. The activity of Wnt signalling and the expression level of Wnt target genes and beta-catenin were determined by luciferase reporter assay, qPCR, immunoblotting and IHC. RESULTS: Moderate cytotoxicity of GD extract in liver cancer cells was observed. GD extract sensitized Huh7 cells to cisplatin treatment. Interestingly, GD extract inhibited cancer sphere formation and reduced the expression of CSC markers. Importantly, GD extract suppressed Huh7 tumor growth, Ki-67 expression and prolonged the anti-liver cancer effect of cisplatin in vivo. Treatment of GD extract resulted in reductions of Wnt reporter activity and the expression of Wnt target genes. Moreover, suppression of beta-catenin were observed in both GD extract treated Huh7 spheres and xenograft tumors. CONCLUSION: Accordingly, our findings suggest that G. divaricata may target liver CSC by suppressing the Wnt pathway and the combination of G. divaricata and cisplatin could be a candidate regimen for treating HCC.

Yin, P. T., et al. (2016). "Stem cell-based gene therapy activated using magnetic hyperthermia to enhance the treatment of cancer." Biomaterials **81**: 46-57.

Stem cell-based gene therapies, wherein stem cells are genetically engineered to express therapeutic molecules, have shown tremendous potential for cancer applications owing to their innate ability to home to tumors. However, traditional stem cell-based gene therapies are hampered by our current inability to control when the therapeutic genes are actually turned on, thereby resulting in detrimental side effects. Here, we report the novel application of magnetic core-shell nanoparticles for the dual purpose of delivering and activating a heat-inducible gene vector that encodes TNF-related apoptosis-inducing ligand (TRAIL) in adipose-derived mesenchymal stem cells (AD-MSCs). By combining the tumor tropism of the AD-MSCs with the spatiotemporal MCNP-based delivery and activation of TRAIL expression, this platform provides an attractive means with which to enhance our control over the activation of stem cell-based gene therapies. In particular, we found that these engineered AD-MSCs retained their innate ability to proliferate, differentiate, and, most importantly, home to tumors, making them ideal cellular carriers. Moreover, exposure of the engineered AD-MSCS to mild magnetic hyperthermia resulted in the selective expression of TRAIL from the engineered AD-MSCs and, as a result, induced significant ovarian cancer cell death in vitro and in vivo.

Yu, J. (2013). "Intestinal stem cell injury and protection during cancer therapy." Transl Cancer Res **2**(5): 384-396.

Radiation and chemotherapy remain the most effective and widely used cancer treatments. These treatments cause DNA damage and selectively target rapidly proliferating cells such as cancer cells, as well as inevitably cause damage to normal tissues, particularly those undergoing rapid self renewal. The side effects associated with radiation and chemotherapy are most pronounced in the hematopoietic (HP) system and gastrointestinal (GI) tract. These tissues are fast renewing and have a well-defined stem cell compartment that plays an essential role in homeostasis, and in treatment-induced acute injury that is dose limiting. Using recently defined intestinal stem cell markers and mouse models, a great deal of insight has been gained in the biology of intestinal stem cells (ISCs), which will undoubtedly help further mechanistic understanding of their injury. This review will cover historic discoveries and recent advances in the identification and characterization of intestinal stem cells, their responses to genotoxic stress, and a new crypt and intestinal stem cell culture system. The discussion will include key pathways regulating intestinal crypt and stem cell injury and regeneration caused by cancer treatments, and strategies for their protection. The focus will be on the acute phase of cell killing in mouse radiation models, where our understanding of the mechanisms in relation to intestinal stem cells is most advanced and interventions appear most effective.

Zhang, S., et al. (2014). "Ovarian cancer stem cells express ROR1, which can be targeted for anti-cancer-stem-cell therapy." Proc Natl Acad Sci U S A **111**(48): 17266-17271.

Although initially responsive to chemotherapy, many patients with ovarian cancer subsequently develop relapsed and potentially fatal metastatic disease, which is thought to develop from cancer stem cells (CSCs) that are relatively resistant to conventional therapy. Here, we show that CSCs express a type I receptor tyrosine kinase-like orphan receptor (ROR1), which is expressed during embryogenesis and by many different cancers, but not normal postpartum tissues. Ovarian cancers with high levels of ROR1 had stem cell-like gene-expression signatures. Furthermore, patients with ovarian cancers with high levels of ROR1 had higher rates of relapse and a shorter median survival than patients with ovarian cancers that expressed low-to-negligible amounts of ROR1. We found that ROR1-positive (ROR1(+)) cells isolated from primary tumor-derived xenografts (PDXs) also expressed aldehyde dehydrogenase 1 (ALDH1) and had a greater capacity to form spheroids and to engraft immune-deficient mice than did ROR1-negative (ROR1(Neg)) ovarian cancer cells isolated from the same tumor population. Treatment with UC-961, an anti-ROR1 mAb, or shRNA silencing of ROR1 inhibited expression of the polycomb ring-finger oncogene, Bmi-1, and other genes associated with the epithelial-mesenchymal transition. Moreover, shRNA silencing of ROR1, depletion of ROR1(+) cells, or treatment with UC-961 impaired the capacity of ovarian cancer cells to form spheroids or tumor xenografts. More importantly, treatment with anti-ROR1 affected the capacity of the xenograft to reseed a virgin mouse, indicating that targeting ROR1 may affect CSC self-renewal. Collectively, these studies indicate that ovarian CSCs express ROR1, which contributes to their capacity to form tumors, making ROR1 a potential target for the therapy of patients with ovarian cancer.

Zhang, X., et al. (2013). "Experimental therapy for lung cancer: umbilical cord-derived mesenchymal stem cell-mediated interleukin-24 delivery." Curr Cancer Drug Targets **13**(1): 92-102.

The use of adult stem cells as gene delivery vehicles is a novel and attractive strategy for cancer therapy. Mesenchymal stem cells (MSCs) provide a promising source for stem cell-based gene therapies. Interleukin-24 (IL24) has been suggested as an effective anticancer agent. However, a lack of tumor-targeted delivery and a host immune response to viral vehicles has hindered its application for cancer therapy. In this study, we evaluated the effects of IL24 delivered by MSCs as a therapeutic approach for lung cancer. We engineered human umbilical cord-derived MSCs (UC-MSCs) to efficiently deliver secretable IL24. We observed that IL24-transduced UC-MSCs (IL24-MSCs) inhibited the growth of A549 lung cancer cells by induction of apoptosis and cell cycle arrest. The IL24 proteins secreted by IL24-MSCs were involved in regulating the ERK-1/2, AKT and JNK signaling pathways. Additionally, MSCs-mediated IL24 expression led to an increase in the cleavage of caspases-3/8/9 and PARP, the Bax/Bcl-2 ratio, as well as the p21 expression in A549 cells. We also demonstrated that injection of IL24-MSCs significantly suppressed xenograft tumor growth. Moreover, the IL24-MSCs had anti-angiogenic effects both in vitro and in vivo. Taken together, our findings indicate that IL24 delivered by human UC-MSCs has the potential to be used as an alternative strategy for lung cancer therapy.

Zhao, Y., et al. (2016). "CD133 expression may be useful as a prognostic indicator in colorectal cancer, a tool for optimizing therapy and supportive evidence for the cancer stem cell hypothesis: a meta-analysis." Oncotarget **7**(9): 10023-10036.

We performed a meta-analysis of CD133-related clinical data to investigate the role of cancer stem cells (CSCs) in the clinical outcomes of colorectal cancer (CRC) patients, analyzing the effectiveness of various therapeutic strategies and examining the validity of the CSC hypothesis. For 28 studies (4546 patients), the relative risk (RR) to survival outcomes associated with CD133+ CRCs were calculated using STATA 12.0 software. Pooled results showed that CD133High patients had poor 5-year overall survival (RR 0.713, 95% CI 0.616-0.826) and 5-year disease free survival (RR 0.707, 95% CI 0.602-0.831). Both associations were consistently observed across different races, research techniques and therapeutic strategies. In a subgroup receiving adjuvant therapy, CD133Low patients achieved significantly better survival than CD133High patients. The findings suggest that CD133 could serve as a predictive marker of poor prognosis and treatment failure in CRC. CD133Low patients could benefit from adjuvant treatments, while CD133High patients should be given novel treatments besides adjuvant therapy. Our results also provide evidence in support of the CSC hypothesis.

Zhu, D., et al. (2014). "Induced pluripotent stem cell-derived neural stem cells transduced with baculovirus encoding CD40 ligand for immunogene therapy in mouse models of breast cancer." Hum Gene Ther **25**(8): 747-758.

The interaction between CD40 ligand (CD40L) and CD40 can directly inhibit growth of CD40-positive carcinoma cells and may indirectly inhibit tumor growth through coordination of immune responses. Many efforts in CD40L cancer gene therapy have been focused on direct CD40L gene transfer into malignant target cells. This in vivo gene

therapy approach relies on high-efficiency gene transfer and could be technically challenging for the treatment of certain cancers, especially multisite metastases. We report herein an alternative means of using the tumor-homing property of neural stem cells (NSCs) to deliver CD40L molecules into tumor tissues. NSCs were derived from human induced pluripotent stem cells, transduced in vitro with a baculoviral vector encoding CD40L, and intravenously injected into immunocompetent mice with orthotopic and metastatic breast cancers. Through a bystander mechanism of intercellular transfer of CD40L from the donor NSCs to tumor target cells, the treatment impeded tumor growth, leading to prolonged survival of the tumor-bearing mice. We further showed that compared with the stem cell-based gene therapy that employed a suicide gene, the CD40L immunogene therapy did not cause liver and kidney injury in the treated mice. This new approach may be particularly valuable for metastatic cancer treatments after systemic stem cell administration.

Zhu, Y., et al. (2014). "Mesenchymal stem cell-based NK4 gene therapy in nude mice bearing gastric cancer xenografts." Drug Des Devel Ther **8**: 2449-2462.

Mesenchymal stem cells (MSCs) have been recognized as promising delivery vehicles for gene therapy of tumors. Gastric cancer is the third leading cause of worldwide cancer mortality, and novel treatment modalities are urgently needed. NK4 is an antagonist of hepatocyte growth factor receptors (Met) which are often aberrantly activated in gastric cancer and thus represent a useful candidate for targeted therapies. This study investigated MSC-delivered NK4 gene therapy in nude mice bearing gastric cancer xenografts. MSCs were transduced with lentiviral vectors carrying NK4 complementary DNA or enhanced green fluorescent protein (GFP). Such transduction did not change the phenotype of MSCs. Gastric cancer xenografts were established in BALB/C nude mice, and the mice were treated with phosphate-buffered saline (PBS), MSCs-GFP, Lenti-NK4, or MSCs-NK4. The tropism of MSCs toward gastric cancer cells was determined by an in vitro migration assay using MKN45 cells, GES-1 cells and human fibroblasts and their presence in tumor xenografts. Tumor growth, tumor cell apoptosis and intratumoral microvessel density of tumor tissue were measured in nude mice bearing gastric cancer xenografts treated with PBS, MSCs-GFP, Lenti-NK4, or MSCs-NK4 via tail vein injection. The results showed that MSCs migrated preferably to gastric cancer cells in vitro. Systemic MSCs-NK4 injection significantly suppressed the growth of gastric cancer xenografts. MSCs-NK4 migrated and accumulated in tumor tissues after systemic injection. The microvessel density of tumor xenografts was decreased, and tumor cellular apoptosis was significantly induced in the mice treated with MSCs-NK4 compared to control mice. These findings demonstrate that MSC-based NK4 gene therapy can obviously inhibit the growth of gastric cancer xenografts, and MSCs are a better vehicle for NK4 gene therapy than lentiviral vectors. Further studies are warranted to explore the efficacy and safety of the MSC-based NK4 gene therapy in animals and cancer patients.

Zieker, D., et al. (2013). "Induction of tumor stem cell differentiation--novel strategy to overcome therapy resistance in gastric cancer." Langenbecks Arch Surg **398**(4): 603-608.

PURPOSE: Metastases are a frequent finding in gastric cancer and are associated with poor prognosis. A recently discovered link between metabolic changes, differentiation, and therapy resistance due to tumor stem cells could depict a novel approach in cancer research and therapy. Phosphoglycerate kinase 1 (PGK1) is a metabolic enzyme and is known to be involved in enabling gastric cancer cells to be invasive and to disseminate. In this study, we investigated if PGK1 is a promising candidate in inducing stem cell differentiation in gastric cancer. MATERIALS AND METHODS: MKN45 gastric cancer cells were used due to their known cancer stem cell population, which is defined by the surface marker CD44. MKN45 cells were separated between CD44+ and CD44- cells and, in equal parts, incubated with shRNA anti-PGK1 using fluorescence-activated cell sorting (FACS) analysis; they were then injected into nude mice to evaluate their tumor growth behavior in vivo. Further, the invasive potential of gastric cancer cells was evaluated in vitro using the xCelligence analyzing system. RESULTS: CD44+ gastric cancer cells treated with and without shRNA anti-PGK1 were capable to cause tumor growth in vivo, whereas tumor growth in CD44+ cells treated with shRNA anti-PGK1 was considerably smaller in comparison with that in CD44+ cells without treatment. CD44- cells did not show any noticeable tumor growth in vivo. By targeting PGK1, the invasive potential of gastric cancer cells was impressively reduced in vitro. In all our cells, which were targeted with shRNA anti-PGK1, we did not find any change that is in accordance with the phenotype of the cells using FACS analysis. CONCLUSIONS: Our findings suggest that targeting the key metabolic enzyme PGK1 in gastric cancer cells may open a new chapter in cancer treatment, which is well worth for further exploration in combination with recent chemotherapy, and might be a promising possibility to overcome therapy resistance in gastric cancer.

Zimmerlin, L., et al. (2013). "Mesenchymal stem cell secretome and regenerative therapy after cancer." Biochimie **95**(12): 2235-2245.

Cancer treatment generally relies on tumor ablative techniques that can lead to major functional or disfiguring defects. These post-therapy impairments require the development of safe regenerative therapy strategies during cancer remission. Many current tissue repair approaches exploit paracrine (immunomodulatory, pro-angiogenic, anti-apoptotic and pro-survival effects) or restoring (functional or structural tissue repair) properties of mesenchymal stem/stromal cells (MSC). Yet, a major concern in the application of regenerative therapies during cancer remission remains the possible triggering of cancer recurrence. Tumor relapse implies the persistence of rare subsets of tumor-initiating cancer cells which can escape anti-cancer therapies and lie dormant in specific niches awaiting reactivation via unknown stimuli. Many of the components required for successful regenerative therapy (revascularization, immunosuppression, cellular homing, tissue growth promotion) are also critical for tumor progression and metastasis. While bi-directional crosstalk between tumorigenic cells (especially aggressive cancer cell lines) and MSC (including tumor stroma-resident populations) has been demonstrated in a variety of cancers, the effects of local or systemic MSC delivery for regenerative purposes on persisting cancer cells during remission remain controversial. Both pro- and anti-tumorigenic effects of MSC have been reported in the literature. Our own data using breast cancer clinical isolates have suggested that dormant-like tumor-initiating cells do not respond to MSC signals, unlike actively dividing cancer cells which benefited from the presence of supportive MSC. The secretome of MSC isolated from various tissues may partially diverge, but it includes a core of cytokines (i.e. CCL2, CCL5, IL-6, TGFbeta, VEGF), which have been implicated in tumor growth and/or metastasis. This article reviews published models for studying interactions between MSC and cancer cells with a focus on the impact of MSC secretome on cancer cell activity, and discusses the implications for regenerative therapy after cancer.

Zuo, Z. Q., et al. (2016). "Promoting tumor penetration of nanoparticles for cancer stem cell therapy by TGF-beta signaling pathway inhibition." Biomaterials **82**: 48-59.

Cancer stem cells (CSCs), which hold a high capacity for self-renewal, play a central role in the development, metastasis, and recurrence of various malignancies. CSCs must be eradicated to cure instances of cancer; however, because they can reside far from tumor vessels, they are not easily targeted by drug agents carried by nanoparticle-based drug delivery systems. We herein demonstrate that promoting tumor penetration of nanoparticles by transforming growth factor beta (TGF-beta) signaling pathway inhibition facilitates CSC therapy. In our study, we observed that although nanoparticles carrying siRNA targeting the oncogene polo-like kinase 1 (Plk1) efficiently killed breast CSCs derived from MDA-MB-231 cells in vitro, this intervention enriched CSCs in the residual tumor tissue following systemic treatment. However, inhibition of the TGF-beta signaling pathway with LY364947, an inhibitor of TGF-beta type I receptor, promoted the penetration of nanoparticles in tumor tissue, significantly ameliorating the intratumoral distribution of nanoparticles in MDA-MB-231 xenografts and further leading to enhanced internalization of nanoparticles by CSCs. As a result, synergistic treatment with a nanoparticle drug delivery system and LY364947 inhibited tumor growth and reduced the proportion of CSCs in vivo. This study suggests that enhanced tumor penetration of drug-carrying nanoparticles can enhance CSCs clearance in vivo and consequently provide superior anti-tumor effects.

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