Stem Cell Transplantation 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 stem cell transplantation related studies.

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Key words: stem cell; 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.

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

Abid, M. B., S. De Mel, et al. "Bortezomib-related Neuropathy masking CNS relapse in Multiple Myeloma; A unique case report and review of the Literature." Cancer Biol Ther. 2016 Apr 22:0.

BACKGROUND: Neuropathy is a common adverse effect of bortezomib. Isolated central nervous system (CNS) relapse in MM remains exceedingly rare and carries a dismal prognosis. We present an unusual case of bortezomib related neuropathy masking a CNS relapse of MM. PRESENTATION: A 57-year-old female was diagnosed with standard-risk MM with clinical and cytogenetic features not typically associated with CNS involvement. She was treated with four cycles of bortezomib/cyclophosphamide/dexamethasone (VCD) and achieved a VGPR, after which she underwent an autologous stem cell transplant (ASCT) followed by bortezomib maintenance. Six months after ASCT she developed symptoms suggestive of peripheral neuropathy which was attributed to bortezomib. However the symptoms persisted despite discontinuation of bortezomib. Imaging and cerebrospinal fluid analysis subsequently confirmed a CNS relapse. DISCUSSION: CNS involvement in MM (CNS-MM) is uncommon and is considered an aggressive disease. Recently published literature has reported biomarkers with prognostic potential. However, isolated CNS relapse is even less common; an event which carries a very poor prognosis. Given the heterogeneous neurologic manifestations associated with MM, clinical suspicion may be masked by confounding factors such as bortezomib-based therapy. The disease may further remain incognito if the patient does not exhibit any of the high risk features and biomarkers associated with CNS involvement. CONCLUSION: In the era of proteasome inhibitor (PI)/immunomodulator (IMID)-based therapy for MM which carries neurologic adverse effects, it is prudent to consider CNS relapse early. This case further highlights the need for more robust biomarkers to predict CNS relapse and use of newer novel agents which demonstrate potential for CNS penetration.

Alchalby, H., D. R. Yunus, et al. "A phase II, single-arm, prospective study of bendamustine plus melphalan conditioning for second autologous stem cell transplantation in de novo multiple myeloma patients through a tandem transplant strategy." Bone

Marrow Transplant. 2016 Apr 18. doi: 10.1038/bmt.2016.98.

This phase II trial evaluates, for the first time, the safety and efficacy of bendamustine plus high-dose melphalan (HDM) as a conditioning regimen before the second autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM) patients. In total, 32 ASCT patients received HDM (200 mg/m2) as conditioning for the first ASCT. After 3-6 months from the first ASCT, responding patients underwent a second ASCT following bendamustine (200 mg/m2) and HDM (140 mg/m2). High-dose chemotherapy and ASCT were performed with complete neutrophil and platelet recovery in all patients. The median number of days to neutrophil and platelet engraftment was 11 (range 9-15) and 12 (range 10-19), respectively. Only one subject experienced grade 3 diarrhea; the rate of mucositis and vomiting was significantly lower with the bendamustine plus HDM regimen compared with the HDM-only regimen (81.2 vs 96.9%, P=0.025 and 78.1 vs 100%, P=0.008). Overall response rate (ORR) was 81.2% after the first transplant, and 90.6% after the second, while complete response rates were 46.8 and 62.5%, respectively (P=0.016). Actuarial 2-year PFS and OS were 79% (95% confidence interval (CI), 60-98) and 97% (95% CI, 91-100), respectively. Bendamustine+HDM is feasible as the conditioning regimen for second ASCT in MM patients. The present study may pave the way for phase III studies specifically aimed at further investigating this combination strategy. The role of this combination in MM for conditioning regimen in a first or single ASCT setting should be also investigated.Bone Marrow Transplantation advance online publication, 18 April 2016; doi:10.1038/bmt.2016.94.

Asri, A., J. Sabour, et al. "Patients with classical Hodgkin lymphoma experiencing disease progression after treatment with brentuximab vedotin have poor outcomes." EXCLI J. 2016 Feb 15;15:134-43. doi: 10.17179/excli2014-585. eCollection 2016.

BACKGROUND: Brentuximab vedotin (BV) is a key therapeutic agent for patients with relapsed/refractory classical Hodgkin lymphoma (cHL). The outcomes of patients experiencing disease progression after BV are poorly described. PATIENTS AND METHODS: We reviewed our institutional database to identify patients with cHL treated with BV who were either refractory to treatment or experienced disease relapse. We collected clinicopathologic features, treatment details at progression and outcome. RESULTS: 100 patients met inclusion criteria, with median age 32 years (range 18-84) at progression after BV. The median number of treatments prior to BV was 3 (range 0-9); 71 had prior autologous stem-cell-transplant. The objective-response-rate (ORR) to BV was 57%, and the median duration-of-BV-therapy was 3 months (range 1-25). After disease progression post-BV, the most common treatment strategies were investigational agents (n=30), gemcitabine (n=15) and bendamustine (n=12). The cumulative ORR to therapy was 33% (CR 15%). After a median follow-up of 25 months (range 1-74) the median progression-free (PFS) and overall survival (OS) were 3.5 and 25.2 months respectively. By multivariate analysis, no factors analyzed were predictive of PFS; age at progression >45 years and serum albumin <40g/L at disease progression was associated with increased risk of death. Among patients who achieved response to therapy, allogeneic stem cell transplantation was associated with a non-significant trend toward superior OS (P=0.11). CONCLUSIONS: Patients with BV-resistant cHL have poor outcomes. These data serve as a reference for newer agents active in BV-resistant disease.

Atallah, M. R., S. Palioura, et al. "In support of upfront stem cell transplantation as first-line therapy for paediatric patients with idiopathic severe aplastic anaemia who lack a sibling donor." Clin Ophthalmol. 2016 Apr 1;10:593-602. doi: 10.2147/OPTH.S83676. eCollection 2016.

Regeneration of the corneal surface after an epithelial insult involves division, migration, and maturation of a specialized group of stem cells located in the limbus. Several insults, both intrinsic and extrinsic, can precipitate destruction of the delicate microenvironment of these cells, resulting in limbal stem cell deficiency (LSCD). In such cases, reepithelialization fails and conjunctival epithelium extends across the limbus, leading to vascularization, persistent epithelial defects, and chronic inflammation. In partial LSCD, conjunctival epitheliectomy, coupled with amniotic membrane transplantation, could be sufficient to restore a healthy surface. In more severe cases and in total LSCD, stem cell transplantation is currently the best curative option. Before any attempts are considered to perform a limbal stem cell transplantation procedure, the ocular surface must be optimized by controlling causative factors and comorbid conditions. These factors include adequate eyelid function or exposure, control of the ocular surface inflammatory status, and a well-lubricated ocular surface. In cases of unilateral LSCD, stem cells can be obtained from the contralateral eye. Newer techniques aim at expanding cells in vitro or in vivo in order to decrease the need for large limbal resection that may jeopardize the "healthy" eye. Patients with bilateral disease can be treated using allogeneic tissue in combination with

systemic immunosuppressive therapy. Another emerging option for this subset of patients is the use of noncorneal cells such as mucosal grafts. Finally, the use of keratoprosthesis is reserved for patients who are not candidates for any of the aforementioned options, wherein the choice of the type of keratoprosthesis depends on the severity of the disease. In summary, limbal stem cell transplantation improves both vision and quality-of-life in patients with ocular surface disorders associated with LSCD, and overall, the use of autologous tissue offers the best results. Future studies aim at improving cellular expansion and finding different sources of stem cells.

Bouligand, J., C. Richard, et al. "L-asparaginase-based regimens followed by allogeneic hematopoietic stem cell transplantation improve outcomes in aggressive natural killer cell leukemia." Pharm Res. 2016 Apr 18.

Aggressive nature killer cell leukemia (ANKL) is a mature NK-T cell lymphoma with worse prognosis, but optimal treatment is unclear. Therefore, we analyzed the efficacy of L-asparaginase-based regimens for ANKL patients. Twenty-one patients who received dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE) or etoposide, ifosfamide, dexamethasone, and L-asparaginase (VIDL) chemotherapy at Samsung Medical Center were selected. The overall response rate for all patients was 33 % (7/21); 38 % (5/13) in SMILE and 40 % (2/5) in VIDL, respectively. The median progression-free survival was 3.9 months (95 % CI 0.0-8.1 months) and median overall survival was 7.0 months (95 % CI 2.3-11.7 months). Treatment response (P = 0.001), hematopoietic stem cell transplantation (HSCT) (P = 0.007) and negative conversion of Epstein-Barr virus (EBV) DNA titer after treatment (P = 0.004) were significantly associated with survival. Thus, L-asparaginase-based regimens followed by allogeneic HSCT seem to improve the outcome for ANKL patients.

Brocqueville, G., R. S. Chmelar, et al. "Sequential intensified conditioning followed by prophylactic DLI could reduce relapse of refractory acute leukemia after allo-HSCT." Oncotarget. 2016 Apr 12. doi: 10.18632/oncotarget.8709.

The major obstacle is leukemia relapse for refractory leukemia undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). We previously introduced a strategy of sequential intensified conditioning and early rapid immunosupressant withdrawal for refractory leukemia undergoing allo-HSCT, with 5-year overall survival (OS) and 3-year relapse rate of 44.6% and 33.3%. To reduce leukemia relapse, prophylactic donor lymphocyte infusion (DLI) was administered based on our historical strategy. A total of 153 refractory advanced acute leukemia patients were enrolled in this prospective study. According to the availability of donor lymphocytes and the criteria for DLI, 144 patients surviving day +60 were divided into two groups (80 DLI versus 64 non-DLI). The relapse rate was less and OS was better in patients receiving DLI than in those not receiving DLI (22.7% vs 33.9%, P=0.048; 58.1% vs 54.9%, P=0.043). The non-relapse mortality (NRM) was similar between DLI and non-DLI groups (P=0.104). Overall, the 5-year overall and disease-free survival post-transplantation were 51.1%+/-5.7% and 49.2%+/-5.3%. The 5-year relapse rate and NRM were 27.3%+/-4.4% and 29.7%+/-5.3%. Multivariate analysis revealed that lower bone marrow blasts on day 0, DLI and chronic graft-versus-host disease were associated with less relapse and better OS. The strategy of sequential intensified conditioning followed by early immunosupressant withdrawal and DLI could reduce relapse of refractory acute leukemia after allo-HSCT and improve survival.

Byrne, M. and B. N. Savani "Incidence and risk factors of poor graft function after allogeneic stem cell transplantation for myelofibrosis." Bone Marrow Transplant. 2016 Apr 18. doi: 10.1038/bmt.2016.106.

Allogeneic hematopoieteic stem cell transplantation (HSCT) is the only curative treatment for myelofibrosis (MF), but it is still associated with significant risks and complications. One of these complications is poor graft function, but incidence and risk factors have not been studied yet. We retrospectively studied a cohort of 100 patients with primary MF or post-ET/PV MF who received a reduced-intensity HSCT in our center. The cumulative incidence of primary leukocyte engraftment was 98%. The cumulative incidence of poor graft function was 17% and all of the cases occurred before day 100 after HSCT at a median of 49 days (range 24-99 days). In the univariate analysis, age as continuous parameter (P=0.05; hazard ratio 1042) and persistence of significant splenomegaly (defined as palpable splenomegaly of 10 cm under costal margin) at d+30 after HSCT (33% vs 12%; P=0.05) showed an increased cumulative incidence of poor graft function. In conclusion, the incidence of poor graft function after HSCT for MF is rather high, but did not influence survival. Persistence of splenomegaly after transplantation is a significant factor for poor graft function in myelofibrosis patients. Whether therapeutic reduction of splenomegaly before HSCT would result in a lower incidence of poor graft function should be investigated in future studies.Bone Marrow Transplantation advance online publication, 18 April 2016; doi:10.1038/bmt.2016.98.

Cooling, L., S. Hoffmann, et al. "Microchip Screening Platform for Single Cell Assessment of NK Cell Cytotoxicity." J Clin Apher. 2016 Apr 19. doi: 10.1002/jca.21465.

Here, we report a screening platform for assessment of the cytotoxic potential of individual natural killer (NK) cells within larger populations. Human primary NK cells were distributed across a silicon-glass microchip containing 32,400 individual microwells loaded with target cells. Through fluorescence screening and automated image analysis, the numbers of NK and live or dead target cells in each well could be assessed at different time points after initial mixing. Cytotoxicity was also studied by time-lapse live-cell imaging in microwells quantifying the killing potential of individual NK cells. Although most resting NK cells (approximately 75%) were non-cytotoxic against the leukemia cell line K562, some NK cells were able to kill several (>/=3) target cells within the 12-h long experiment. In addition, the screening approach was adapted to increase the chance to find and evaluate serial killing NK cells. Even if the cytotoxic potential varied between donors, it was evident that a small fraction of highly cytotoxic NK cells were responsible for a substantial portion of the killing. We demonstrate multiple assays where our platform can be used to enumerate and characterize cytotoxic cells, such as NK or T cells. This approach could find use in clinical applications, e.g., in the selection of donors for stem cell transplantation or generation of highly specific and cytotoxic cells for adoptive immunotherapy.

Dauwe, D., B. Pelacho, et al. "The Potential and Limits of Hematopoietic Stem Cell Transplantation for the Treatment of Autosomal Dominant Hyper-IgE Syndrome." J Am Heart Assoc. 2016 Apr 18;5(4). pii: e002288. doi: 10.1161/JAHA.115.002288.

PURPOSE: Autosomal dominant hyper-IgE syndrome (AD-HIES) is included among primary immunodeficiencies, and results from heterozygous mutations in the signal transduction and activator of transcription 3 (STAT3) gene. AD-HIES leads to impaired Th17 cell differentiation and IL-17 production, and is associated with increased susceptibility to bacteria and fungi. It was reported that several patients with AD-HIES were treated with hematopoietic stem cell transplantation (HSCT). The efficacy of HSCT in treating AD-HIES is variable. This study aims to evaluate the long-term clinical and immunological efficacy of HSCT for AD-HIES. METHODS: We have followed for more than 8 years two patients with AD-HIES who were treated with HSCT. Their ability of IL-17 production was evaluated by flow cytometry. RESULTS: Both patients indicated the normal ability of IL-17 production and their serum IgE levels decreased after HSCT. On the other hand, they suffered from pulmonary complications of AD-HIES such as pneumatoceles and bronchiectasis even after HSCT; however, the frequency of infections was decreased. CONCLUSIONS: Although the dysfunction of STAT3 in non-hematological tissues such as the lungs could not be corrected by HSCT, AD-HIES patients with risk factors for pulmonary complications may benefit from immunological correction by HSCT before severe pulmonary complications occur. Future studies should investigate risk factors for pulmonary complications in AD-HIES patients.

El-Badawy, A. and N. El-Badri "Fludarabine and busulfan as a reduced-toxicity myeloablative conditioning regimen in allogeneic hematopoietic stem cell transplantation for acute leukemia patients." PLoS One. 2016 Apr 13;11(4):e0151938. doi: 10.1371/journal.pone.0151938. eCollection 2016.

The optimal conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in acute leukemia remains undefined. We evaluated the outcomes in 30 patients with acute leukemia who underwent allo-HSCT from human leukocyte antigen-matched donors after conditioning with busulfan and fludarabine (BuFlu). The regimen comprised injection of busulfan 3.2 mg/kg daily on 4 consecutive days and fludarabine 30 mg/m2 daily for 4 doses. All 30 patients achieved hematopoiesis reconstitution with full donor chimerism confirmed by short tandem repeat DNA analysis. The most common regimen-related toxicity was mucositis (86.7%), followed by cytomegalovirus infection (80%). Serious regimen-related toxicities were rare. Acute graft vs. host disease (aGVHD) was detected in 46.7% of the patients; 33.4% had grade I-II aGVHD and 13.3% had grade III-IV aGVHD. Chronic GVHD (cGVHD) was noted in 20% of the patients. The overall survival and disease-free survival rates were 66.7 and 53%, respectively, with a median follow-up of 25 months for surviving patients. Therefore, BuFlu was an effective conditioning regimen with a low rate of transplant-related adverse effects and increased antileukemic effects in patients with acute leukemia undergoing allo-HSCT.

Fricke, A., P. V. Ullrich, et al. "Predictors of Survival in Acute Myeloid Leukemia by Treatment Modality." Stem Cells Int. 2016;2016:6146047. doi: 10.1155/2016/6146047. Epub 2016 Mar 16.

BACKGROUND/AIM: Evaluations of efficacy of treatment modality in analyses on patients with acute myeloid leukemia (AML) often combine chemotherapy and stem cell transplantation (SCT). To account for the effect of SCT and determine the

impact of chemotherapy alone, the National Cancer Data Base from 1998-2011 was analyzed. PATIENTS AND METHODS: Patients with AML from 1998-2011 aged 18-64 years were included. Chi-square analysis was used to assess the association between treatment and factors investigated. The Kaplan-Meier method was used to assess overall survival. Log-rank methods were used to determine factors significant for survival. Multivariable Cox regression analysis was used to determine the effect of chemotherapy alone, and both chemotherapy and SCT on survival while adjusting for other variables. RESULTS: A total of 34,816 patients from the National Cancer Database were eligible for this study. Eighty-four percent of patients received chemotherapy alone, 8.3% no chemotherapy or SCT, and 7.5 % received both chemotherapy and SCT. Five-year survival for patients without chemotherapy without SCT was 12%, survival for the group treated with chemotherapy alone was 37.8% and for those receiving both chemotherapy and SCT was 44.1%. Treatment with chemotherapy only and chemotherapy plus SCT had a hazard ratio for death of 0.42 and 0.35 compared to no chemotherapy or SCT. Advanced age, male sex, Black race, diagnosis prior to 2004, multiple comorbidities, Medicare insurance, Medicaid insurance, no insurance, lower income and low education level, distance less than 30 miles from treatment Center, diagnosis and treatment at same facility, were independently associated with worse survival. CONCLUSION: Survival analysis of AML in the National Cancer Database showed multiple factors to be independently associated with survival. Outcomes based on treatment suggest an improved survival when utilizing chemotherapy and SCT as the primary treatment modality.

Gouignard, N., M. Maccarana, et al. "Musculocontractural Ehlers-Danlos syndrome and neurocristopathies: dermatan sulfate is required for Xenopus neural crest cells to migrate and adhere to fibronectin." Dis Model Mech. 2016 Apr 21. pii: dmm.024661.

Of all live births with congenital anomalies, approximately one-third exhibit deformities of the head and face. Most craniofacial disorders are associated with defects in a migratory stem and progenitor cell population, which is designated the neural crest (NC). Musculocontractural Ehlers-Danlos syndrome (MCEDS) is a heritable connective tissue disorder with distinct craniofacial features; this syndrome comprises multiple congenital malformations that are caused by dysfunction of dermatan sulfate (DS) biosynthetic enzymes, including DS epimerase-1 (DS-epi1). Studies in mice have extended our understanding of DS-epi1 in connective tissue maintenance; however, its role in fetal development is not understood. We demonstrate that DS-epi1 is important for the generation of isolated iduronic acid residues in chondroitin sulfate (CS)/DS proteoglycans in early ITALIC! Xenopusembryos. The knockdown of DS-epi1 does not affect the formation of early NC progenitors; however, it impairs the correct activation of transcription factors involved in the epithelial-mesenchymal transition (EMT) and reduces the extent of NC cell migration, which leads to a decrease in NC-derived craniofacial skeleton, melanocytes, and dorsal fin structures. Transplantation experiments demonstrate a tissue-autonomous role of DS-epi1 in cranial NC cell migration ITALIC! in vivo Cranial NC explant and single cell cultures indicate a requirement of DS-epi1 in cell adhesion, spreading and extension of polarized cell processes on fibronectin. Thus, our work indicates a functional link between DS and NC cell migration. We conclude that NC defects in the EMT and cell migration may account for the craniofacial anomalies and other congenital malformations in MCEDS, which may facilitate the diagnosis and development of therapies for this distressing condition. Moreover, the presented correlations between human DS-epi1 expression and gene sets of mesenchymal character, invasion, and metastasis in neuroblastoma and malignant melanoma suggest an association between DS and NC-derived cancers.

Haus, D. L., L. Lopez-Velazquez, et al. "The clinical features of fatal cyclophosphamide-induced cardiotoxicity in a conditioning regimen for allogeneic hematopoietic stem cell transplantation (allo-HSCT)." Exp Neurol. 2016 Apr 11. pii: S0014-4886(16)30088-7. doi: 10.1016/j.expneurol.2016.04.008.

Cyclophosphamide (CY) cardiotoxicity induces a rare lethal complication associated with its use. The minimum dose for cardiac toxicity is still not known, although there are no reports of CY toxicity at doses of less than 100 mg/kg. There are few studies of CY cardiotoxicity that included a large number of patients who received high-dose CY for conditioning for allogeneic stem cell transplant (allo-HSCT). To elucidate the clinical course, complications, true incidence, and risk factors, the cardiac events of 811 patients who received more than a total of 100 mg/kg of CY as conditioning for allo-HSCT were analyzed. Twelve of 811 recipients (1.5 %) developed fatal cardiac failure induced by CY at a median of 4 (range 2-8) days after the first administration of CY. Regarding the dose of CY, 8.5, 1.2, and 0 % of the patients developed cardiac failure among the patients treated with a total of 200, 120, and 100 mg/kg CY, respectively. On echocardiography, the E/A ratio shows diastolic dysfunction but not the ejection

fraction changed in the early course. Moreover, a short time to the first symptom after the administration of CY tended to be associated with early death (p = 0.09). Eleven patients died from progressive acute cardiac failure at day 7 (5-30) after the first administration of CY, and only one patient survived. In summary, fatal CY cardiotoxicity with allo-HSCT is a rare complication, but it is associated with high mortality. The possibility of CY-induced cardiotoxicity must be considered early after the administration of CY.

Im, H. J., K. N. Koh, et al. "Recent advances in haploidentical hematopoietic stem cell transplantation using ex vivo T cell-depleted graft in children and adolescents." Blood Res. 2016 Mar;51(1):8-16. doi: 10.5045/br.2016.51.1.8. Epub 2016 Mar 25.

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment for children and adolescents with various malignant and non-malignant diseases. While human leukocyte antigen (HLA)-identical sibling donor is the preferred choice, matched unrelated volunteer donor is another realistic option for successful HSCT. Unfortunately, it is not always possible to find a HLA-matched donor for patients requiring HSCT, leading to a considerable number of deaths of patients without undergoing transplantation. Alternatively, allogeneic HSCT from haploidentical family members could provide donors for virtually all patients who need HSCT. Although the early attempts at allogeneic HSCT from haploidentical family donor (HFD) were disappointing, recent advances in the effective ex vivo depletion of T cells or unmanipulated in vivo regulation of T cells, better supportive care, and optimal conditioning regimens have significantly improved the outcomes of haploidentical HSCT. The ex vivo techniques used to remove T cells have evolved from the selection of CD34(+) hematopoietic stem cell progenitors to the depletion of CD3(+) cells, and more recently to the depletion of alphabeta(+) T cells. The recent emerging evidence for ex vivo T cell-depleted haploidentical HSCT has provided additional therapeutic options for pediatric patients with diseases curable by HSCT but has not found a suitable related or unrelated donor. This review discusses recent advances in haploidentical HSCT, focusing on transplant using ex vivo T cell-depleted grafts. In addition, our experiences with this novel approach for the treatment of pediatric patients with malignant and non-malignant diseases are described.

Kotsiou, E., J. Okosun, et al. "TNFRSF14 aberrations in follicular lymphoma increase clinically significant allogeneic T-cell responses." Blood. 2016 Apr 21. pii: blood-2015-10-679191.

Donor T-cell immune responses can eradicate lymphomas after allogeneic hematopoietic stem-cell transplantation, but can also damage healthy tissues resulting in harmful Graft-versus-Host Disease (GvHD). Next-generation sequencing has recently identified many new genetic lesions in follicular lymphoma. One such gene, ITALIC! TNFRSF14, abnormal in 40% of follicular lymphoma patients, encodes the herpes-virus-entry mediator (HVEM) which limits T-cell activation via ligation of B- and T-lymphocyte attenuator. As lymphoma B-cells can act as antigen-presenting cells, we hypothesized that ITALIC! TNFRSF14aberrations that reduce HVEM expression could alter the capacity of follicular lymphoma B-cells to stimulate allogeneic T-cell responses and impact the outcome of allogeneic hematopoietic stem-cell transplantation. In an ITALIC! in vitromodel of alloreactivity, human lymphoma B-cells with ITALIC! TNFRSF14aberrations had reduced HVEM expression and greater alloantigen-presenting capacity than wild-type lymphoma B-cells. The increased immune stimulatory capacity of lymphoma B-cells with ITALIC! TNFRSF14aberrations had clinical relevance, associating with higher incidence of acute GvHD and in patients undergoing allogeneic hematopoietic stem-cell transplantation. Follicular lymphoma patients with ITALIC! TNFRSF14aberrations may benefit from more aggressive immunosuppression to reduce harmful GvHD after transplantation. Importantly, this study is the first to demonstrate the impact of an acquired genetic lesion on the capacity of tumor cells to stimulate allogeneic T-cell immune responses which may have wider consequences for adoptive immunotherapy strategies.

Kramerov, A. A., M. Saghizadeh, et al. "Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial." J Vis Exp. 2016 Apr 7;(110). doi: 10.3791/54058.

BACKGROUND: Prostate cancer is the most common cancer in men, and radical prostatectomy (RP) often results in erectile dysfunction (ED) and a substantially reduced quality of life. The efficacy of current interventions, principal treatment with PDE-5 inhibitors, is not satisfactory and this condition presents an unmet medical need. Preclinical studies using adipose-derived stem cells to treat ED have shown promising results. Herein, we report the results of a human phase 1 trial with autologous adipose-derived regenerative cells (ADRCs) freshly isolated after a liposuction. METHODS: Seventeen men suffering from post RP ED, with no recovery using

conventional therapy, were enrolled in a prospective phase 1 open-label and single-arm study. All subjects had RP performed 5-18 months before enrolment, and were followed for 6 months after intracavernosal transplantation. ADRCs were analyzed for the presence of stem cell surface markers, viability and ability to differentiate. Primary endpoint was the safety and tolerance of the cell therapy while the secondary outcome was improvement of erectile function. Any adverse events were reported and erectile function was assessed by IIEF-5 scores. The study is registered with ClinicalTrials.gov, NCT02240823. FINDINGS: Intracavernous injection of ADRCs was well-tolerated and only minor events related to the liposuction and cell injections were reported at the one-month evaluation, but none at later time points. Overall during the study period, 8 of 17 men recovered their erectile function and were able to accomplish sexual intercourse. Post-hoc stratification according to urinary continence status was performed. Accordingly, for continent men (median IIEFinclusion = 7 (95% CI 5-12), 8 out of 11 men recovered erectile function (IIEF6months = 17 (6-23)), corresponding to a mean difference of 0.57 (0.38-0.85; p = 0.0069), versus inclusion. In contrast, incontinent men did not regain erectile function (median IIEF1/3/6 months = 5 (95% CI 5-6); mean difference 1 (95% CI 0.85-1.18), p > 0.9999). INTERPRETATION: In this phase I trial a single intracavernosal injection of freshly isolated autologous ADRCs was a safe procedure. A potential efficacy is suggested by a significant improvement in IIEF-5 scores and erectile function. We suggest that ADRCs represent a promising interventional therapy of ED following prostatectomy. FUNDING: Danish Medical Research Council, Odense University Hospital and the Danish Cancer Society.

Lopez-Serrano, C., A. Torres-Espin, et al. "Yellow nail syndrome after allogeneic haematopoietic stem cell transplantation in two patients with multiple myeloma." Cell Transplant. 2016 Apr 5.

OBJECTIVE AND IMPORTANCE: Yellow nail syndrome (YNS) is a rare disorder of unknown aetiology characterized by the triad of yellow nails, lymphoedema and respiratory manifestations. About 200 cases have been reported, but a lot of patients probably elude proper diagnosis because of both variability of symptoms and ignorance of this syndrome by many physicians. The pathogenesis remains unclear, and could involve functional lymphatic abnormalities, microvasculopathy or lymphocyte deficiency, but none of these hypotheses seems fully satisfactory. CLINICAL PRESENTATION: We report for the first time two cases of YNS associated with multiple myeloma relapsing after non-myeloablative haematopoietic cell transplantation (HCT). In these two cases, onset or worsening of YNS symptoms followed graft-versus-host disease (GvHD) manifestations. INTERVENTION: Corticosteroids given to treat GvHD also improved YNS manifestations. CONCLUSION: YNS after HCT might be a microvascular manifestation of endothelial GvHD and corticosteroids might be an effective treatment.

Mackarel, J., M. Iatan, et al. Culture conditions have an impact on the maturation of traceable, transplantable mouse embryonic stem cell-derived otic progenitor cells, Br J Haematol. 2016 Apr 21. doi: 10.1111/bjh.14097.

The generation of replacement inner ear hair cells (HCs) remains a challenge and stem cell therapy holds the potential for developing therapeutic solutions to hearing and balance disorders. Recent developments have made significant strides in producing mouse otic progenitors using cell culture techniques to initiate HC differentiation. However, no consensus has been reached as to efficiency and therefore current methods remain unsatisfactory. In order to address these issues, we compare the generation of otic and HC progenitors from embryonic stem (ES) cells in two cell culture systems: suspension vs. adherent conditions. In the present study, an ES cell line derived from an Atoh1-green fluorescent protein (GFP) transgenic mouse was used to track the generation of otic progenitors, initial HCs and to compare these two differentiation systems. We used a two-step short-term differentiation method involving an induction period of 5 days during which ES cells were cultured in the presence of Wnt/transforming growth factor TGF-beta inhibitors and insulin-like growth factor IGF-1 to suppress mesoderm and reinforce presumptive ectoderm and otic lineages. The generated embryoid bodies were then differentiated in medium containing basic fibroblast growth factor (bFGF) for an additional 5 days using either suspension or adherent culture methods. Upon completion of differentiation, quantitative polymerase chain reaction analysis and immunostaining monitored the expression of otic/HC progenitor lineage markers. The results indicate that cells differentiated in suspension cultures produced cells expressing otic progenitor/HC markers at a higher efficiency compared with the production of these cell types within adherent cultures. Furthermore, we demonstrated that a fraction of these cells can incorporate into ototoxin-injured mouse postnatal cochlea explants and express MYO7A after transplantation. Copyright (c) 2016 John Wiley & Sons, Ltd.

Martinez, H. R., M. T. Gonzalez-Garza, et al. Transplantable living scaffolds comprised of micro-tissue engineered aligned astrocyte networks to facilitate central nervous system regeneration, Cytotherapy. 2016 Apr 15. pii: S1465-3249(16)30323-1. doi: 10.1016/j.jcyt.2016.03.294.

Neurotrauma, stroke, and neurodegenerative disease may result in widespread loss of neural cells as well as the complex interconnectivity necessary for proper central nervous system function, generally resulting in permanent functional deficits. Potential regenerative strategies involve the recruitment of endogenous neural stem cells and/or directed axonal regeneration through the use of tissue engineered "living scaffolds" built to mimic features of three-dimensional (3-D) in vivo migratory or guidance pathways. Accordingly, we devised a novel biomaterial encasement scheme using tubular hydrogel-collagen micro-columns that facilitated the self-assembly of seeded astrocytes into 3-D living scaffolds consisting of long, cable-like aligned astrocytic networks. Here, robust astrocyte alignment was achieved within a micro-column inner diameter of 180mum or 300-350mum but not 1.0mm, suggesting that radius of curvature dictated the extent of alignment. Moreover, within small ID micro-columns, >70% of the astrocytes assumed a bi-polar morphology, versus approximately 10% in larger micro-columns or planar surfaces. Cell-cell interactions also influenced the aligned architecture, as extensive astrocyte-collagen contraction was achieved at high (9-12x105cells/mL) but not lower (2-6x105cells/mL) seeding densities. This high density micro-column seeding led to the formation of ultra-dense 3-D "bundles" of aligned bi-polar astrocytes within collagen measuring up to 150mum in diameter yet extending to a remarkable length of over 2.5cm. Importantly, co-seeded neurons extended neurites directly along the aligned astrocytic bundles, demonstrating permissive cues for neurite extension. These transplantable cable-like astrocytic networks structurally mimic the glial tube that guides neuronal progenitor migration in vivo along the rostral migratory stream, and therefore may be useful to guide progenitor cells to repopulate sites of widespread neurodegeneration. STATEMENT OF SIGNIFICANCE: This manuscript details our development of novel micro-tissue engineering techniques to generate robust networks of longitudinally aligned astrocytes within transplantable microcolumn hydrogels. We report a novel biomaterial encasement scheme that facilitated the selfassembly of seeded astrocytes into long, aligned regenerative pathways. These miniature "living scaffold" constructs physically emulate the glial tube - a pathway in the brain consisting of aligned astrocytes that guide the migration of neuronal progenitor cells - and therefore may facilitate directed neuronal migration for central nervous system repair. The small size and selfcontained design of these aligned astrocyte constructs will permit minimally invasive transplantation of the living micro-columns in models of central nervous system injury in future studies.

Miller, E. B., R. Grosu, et al. "The Prognosis Of Adult Burkitt's Cell Leukemia In Real-Life Clinical Practice." Clin Rheumatol. 2016 Apr 19.

INTRODUCTION: Many studies reported an improved prognosis in the patients with Burkitt's lymphoma obviating the need of stem cell transplantation. However, prognosis of the advanced disease (i.e. Burkitt's cell leukemia) has not been reported with current treatment modalities except for a few prospective trials. The aim of this study is to compare the prognoses of the Burkitt's cell leukemia (BL) patients with similarly treated and not transplanted other types of acute lymphoblastic leukemia (ALL) patients and with ALL cases that underwent allogeneic stem cell transplantation (ASCT) in their first remissions. METHODS: In this retrospective analysis, BL patients aged between 16 and 63 who admitted between 2000 and 2014 to Hacettepe or Gazi University Hospitals and treated with intensive therapies aiming cure were included in the study. All ALL patients who were treated with a similar protocol not including transplantation during the same period (NTxALL group) and all ALL patients who underwent ASCT in first complete remission during the same period (TxALL group) were gathered as control groups. RESULTS: The central nervous system or extra-medullary involvement rate, LDH levels and white blood cell count at diagnosis was higher in BL group than NTxALL group and these differences were significant. BL patients had DFS durations comparable with the TxALL cohort but, NTxALL cases had significantly inferior DFS durations. Both cumulative relapse incidence and cumulative non-relapse mortality were higher in NTxALL patients compared to TxALL group and BL patients. DISCUSSION AND CONCLUSION: DFS in BL patients treated with a widely accepted modern regimen, R-HyperCVAD, is comparable to allogeneic transplanted other ALL patients. Our results are in agree with few prospective non-comparative studies suggesting no further need in stem cell transplantation in BL.

Nakano, H., M. Ashizawa, et al. "Efficacy of upfront high-dose chemotherapy plus rituximab followed by autologous peripheral blood stem cell transplantation for untreated high-intermediate-, and high-risk diffuse

large B-cell lymphoma: a multicenter prospective phase II study (JSCT-NHL04)." Int J Hematol. 2016 Apr 15.

To evaluate the efficacy and feasibility of upfront high-dose chemotherapy (HDCT) and rituximab (R) followed by autologous peripheral blood stem cell transplantation (auto-PBSCT) in patients with newly diagnosed high-intermediate(HI)-, and high(H)-risk diffuse large B-cell lymphoma (DLBCL), we conducted a multicenter prospective phase II trial. In 15-60-year-old patients with H- or HI-risk DLBCL, after three courses of (R-)CHOP14, high-dose etoposide was given prior to peripheral blood stem cell harvesting. After an additional three courses of (R-)CHOP14, auto-PBSCT was performed following HDCT. The primary endpoint of the study is progression-free survival (PFS) at 2 years after registration in eligible patients. The expected PFS and the threshold PFS were estimated to be 70 and 50 %, respectively. Among 40 eligible patients registered, 30 patients completed treatment. With a median observation period in surviving eligible patients of 63 months, the 2- and 4-year PFS after registration were 79.9 and 72.0 %, respectively.

Ozen, M., C. Ustun, et al. "Retrospective Study of Incidence and Prognostic Significance of Eosinophilia after Allogeneic Hematopoietic Stem Cell Transplantation: Influence of Corticosteroid Therapy." Turk J Haematol. 2016 Apr 18. doi: 10.4274/tjh.2015.0346.

OBJECTIVE: The clinical significance of eosinophilia after allogeneic hematopoietic stem cell transplantation is controversial. MATERIALS AND METHODS: We retrospectively studied 204 patients with acute myeloid leukemia, acute lymphoblastic leukemia and myelodysplastic syndrome who underwent allogeneic hematopoietic stem cell transplantation from January 2001 to December 2010. RESULTS: The median age was 43 years (range: 17-65 years). Myeloablative conditioning was used in 153 patients and reduced intensity conditioning was employed in 51 patients. Donor cells were from bone marrow in 132 patients, peripheral blood in 34, and cord blood in 38. Eosinophilia was detected in 71 patients and there was no significant predictor of eosinophilia by multivariate analysis. There was no relationship between occurrence of eosinophilia and the incidence or grade of acute graft-versus-host disease when the patients stratified according to corticosteroid treatment. Although eosinophilia was a prognostic factor for 5-year overall survival by univariate analysis, it was not a significant indicator by multivariate analysis. CONCLUSION: These results suggest that the clinical significance of eosinophilia in patients receiving allogeneic hematopoietic stem cell transplantation should be assessed with consideration of systemic corticosteroid administration.

Pal, D., H. J. Blair, et al. "Long-term in vitro maintenance of clonal abundance and leukaemia-initiating potential in acute lymphoblastic leukaemia." Leukemia. 2016 Apr 25. doi: 10.1038/leu.2016.79.

Lack of suitable in vitro culture conditions for primary acute lymphoblastic leukaemia (ALL) cells severely impairs their experimental accessibility and the testing of new drugs on cell material reflecting clonal heterogeneity in patients. We show that Nestin-positive human mesenchymal stem cells (MSC) support expansion of a range of biologically and clinically distinct patient-derived ALL samples. Adherent ALL cells showed an increased accumulation in the S-phase of the cell cycle and diminished apoptosis when compared to cells in the suspension fraction. Moreover, surface expression of adhesion molecules CD34, CDH2 and CD10 increased several folds. About 20% of the ALL cells were in G0 phase of the cell cycle suggesting that MSCs may support quiescent ALL cells. Cellular barcoding demonstrated long-term preservation of clonal abundance. Expansion of ALL cells for more than 3 months compromised neither feeder dependence nor cancer initiating ability as judged by their engraftment potential in immunocompromised mice. doi:10.1038/leu.2016.79.

Pellegrini, G., A. Lambiase, et al. "Significance of AZD1152 as a potential treatment against Aurora B overexpression in acute promyelocytic leukemia." Regen Med. 2016 Apr 19.

Aurora B kinase as a chromosomal passenger protein plays multiple roles in regulating mitosis and cytokinesis. The function of Aurora B in leukemic cells has made it an important treatment target. In this study, we explored the expressions of Aurora (A, B, and C) kinases in newly diagnosed acute promyelocytic leukemia (APL) patients. In addition, we investigated the effects of AZD1152 as a specific inhibitor of Aurora B on cell survival, DNA synthesis, nuclear morphology, apoptosis induction, cell cycle distribution, and gene expression in an APL-derived NB4 cell line. Our results showed that Aurora B was overexpressed in 88 % of APL patients. AZD1152 treatment of NB4 cells led to viability reduction and G2/M arrest followed by an increase in cell size and polyploidy induction. These giant cells showed morphological evidence of mitotic catastrophe. AZD1152 treatment induced activation of G2/M checkpoint which in turn led to transient G2/M arrest in a p21-independent manner. Lack of functional p53 in NB4 cells might provide an opportunity to escape

from G2/M block and to endure repeated rounds of replication and polyploidy. Treated cells were probably eliminated via p73-mediated overexpression of BAX, PUMA, and APAF1 and downregulation of survivin and MCL-1. In summary, AZD1152 treatment led to endomitosis and polyploidy in TP53-mutated NB4 cells. These giant polyploid cells might undergo mitotic catastrophe and p73-mediated apoptosis. It seems that induction of polyploidy via AZD1152 could be a novel form of anti-cancer therapy for APL that may be clinically accessible in the near future.

Pietras, E. M., C. Mirantes-Barbeito, et al. "Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal." Nat Cell Biol. 2016 Apr 25. doi: 10.1038/ncb3346.

Haematopoietic stem cells (HSCs) maintain lifelong blood production and increase blood cell numbers in response to chronic and acute injury. However, the mechanism(s) by which inflammatory insults are communicated to HSCs and their consequences for HSC activity remain largely unknown. Here, we demonstrate that interleukin-1 (IL-1), which functions as a key pro-inflammatory 'emergency' signal, directly accelerates cell division and myeloid differentiation of HSCs through precocious activation of a PU.1-dependent gene program. Although this effect is essential for rapid myeloid recovery following acute injury to the bone marrow, chronic IL-1 exposure restricts HSC lineage output, severely erodes HSC self-renewal capacity, and primes IL-1-exposed HSCs to fail massive replicative challenges such as transplantation. Importantly, these damaging effects are transient and fully reversible on IL-1 withdrawal. Our results identify a critical regulatory circuit that tailors HSC responses to acute needs, and is likely to underlie deregulated blood homeostasis in chronic inflammation conditions.

Riwes, M. M., H. Leather, et al. "Prognostic factors and outcomes for pediatric patients receiving an haploidentical relative allogeneic transplant using CD3/CD19-depleted grafts." Bone Marrow Transplant. 2016 Apr 18. doi: 10.1038/bmt.2016.92.

Haploidentical hematopoietic stem cell transplantation using T-cell-depleted grafts is a valid option for pediatric patients with hematological malignancies in need of an allogeneic transplantation and lacking an HLA-identical donor. Seventy-five transplantations were performed in 70 patients. Thirty-eight patients had ALL, 32 had AML, 3 had advanced myelodysplastic syndromes and 2 juvenile myelomonocytic leukemia; 19 were in first CR, 30 in second CR, 12 in greater than second CR and 14 were considered to be in refractory disease at time of transplantation. Four patients developed graft failure. Among engrafted patients, the median time to neutrophil and platelet recovery was 13 (range 8-20) and 10 days (range 8-70), respectively. In 64 (85%) cases, 1 infections were diagnosed after transplant. The probability of nonrelapse mortality by day +100 after transplantation was 10+/-4%. With a median follow-up of 22 months, the probability of relapse was 32+/-6% and disease-free survival was 52+/-6%. Haploidentical transplantation using CD3/CD19 depletion is associated with encouraging results especially in patients in early phase of disease. Killer-cell Ig-like receptor B haplotype donors confer a rapid natural killer cells expansion early after transplantation, resulting in lower probability of relapse and suggesting a GvL effect apart from graft-versus-host reactions. Donor infusion of high numbers of CD34+ cells is recommended in order to improve T-cell reconstitution.Bone Marrow Transplantation advance online publication, 18 April 2016; doi:10.1038/bmt.2016.101.

Rodriguez-Pallares, J., A. I. Rodriguez-Perez, et al. "Distinct bone marrow blood vessels differentially regulate haematopoiesis." Stem Cells Transl Med. 2016 Apr 13. pii: sctm.2015-0182.

Bone marrow endothelial cells (BMECs) form a network of blood vessels that regulate both leukocyte trafficking and haematopoietic stem and progenitor cell (HSPC) maintenance. However, it is not clear how BMECs balance these dual roles, and whether these events occur at the same vascular site. We found that mammalian bone marrow stem cell maintenance and leukocyte trafficking are regulated by distinct blood vessel types with different permeability properties. Less permeable arterial blood vessels maintain haematopoietic stem cells in a low reactive oxygen species (ROS) state, whereas the more permeable sinusoids promote HSPC activation and are the exclusive site for immature and mature leukocyte trafficking to and from the bone marrow. A functional consequence of high permeability of blood vessels is that exposure to blood plasma increases bone marrow HSPC ROS levels, augmenting their migration and differentiation, while compromising their long-term repopulation and survival. These findings may have relevance for clinical haematopoietic stem cell transplantation and mobilization protocols.

Roellecke, K., E. L. Virts, et al. "Procedure-related complications and adverse events associated with pediatric autologous peripheral blood stem cell

collection." Gene Ther. 2016 Apr 19. doi: 10.1038/gt.2016.38.

INTRODUCTION: Autologous peripheral blood hematopoietic progenitor cell collection (A-HPCC) in pediatric patients is considered relatively safe although technically challenging. Very little is known regarding the incidence, risk factors and impact of procedure-related adverse events (AE) on pediatric A-HPCC outcomes. METHODS: Prospective 4.5-year review of AE associated with pediatric A-HPCC. AE were graded by severity and type. Potential demographic and procedural risk factors, and the impact on product quality, were compared by t-test, chi-square, and linear regression. RESULTS: Sixty-two children underwent 110 A-HPCC, including 36 (58%) under 20 kg. Fifty-five AE were documented in 25.4% A-HPCCs and 39% of children (citrate 25%, access 19%, technical 11%, cardiovascular 0%, allergic 1.8%). No AE were noted in children < 10 kg anticoagulated with heparin. Access and technical AE accounted for 73% of severe AE, with line-related problems underlying most technical AE (87.5%, P = 0.006). AE were more likely in older (P = 0.012), heavier patients (P = 0.02), who frequently required more than one A-HPCC (P = 0.012). In contrast, young children were more likely to experience citrate AE with gastrointestinal symptoms (median age, 6 years; P = 0.076). AE had no impact on CD34 collection rates; however, mean CD34 yields (4.2 vs. 20.4 million/kg; P = 0.0035) were decreased in patients with technical AE due to lower peripheral CD34 counts and a high number of aborted procedures (37%). CONCLUSION: Venous access and flow-related issues are a major factor associated with moderate and severe AE, effecting approximately 10% of patients. AE are more frequent with increasing patient age, weight, and number of procedures. J. Clin. Apheresis, 2016. (c) 2016 Wiley Periodicals, Inc.

Romano, M., D. E. F. F, et al. "Analysis of bone-cartilage-stromal progenitor populations in trauma induced and genetic models of heterotopic ossification." Anticancer Res. 2016 Apr;36(4):1447-60.

Heterotopic ossification (HO), the formation of extra-skeletal bone in soft tissues, is a pathologic process occurring after substantial burns or trauma, or in patients with type I bone morphogenetic protein (BMP) receptor hyperactivating mutations. Identifying the cells responsible for de novo bone formation during adulthood is of critical importance for therapeutic and regenerative purposes. Using a model of trauma-induced HO with hindlimb Achilles' tenotomy and dorsal burn injury and a genetic non-trauma HO model (Nfatc1-Cre/caAcvr1fl/wt), we demonstrate enrichment of previously defined bone-cartilage-stromal progenitor cells (BCSP: AlphaV+/CD105+/Tie2-/CD45-/Thy1-/6C3-) at the site of HO formation when compared with marrow isolated from the ipsilateral hindlimb, or from tissue of the contralateral, uninjured hindlimb. Upon transplantation into tenotomy sites soon after injury, BCSPs isolated from neonatal mice or developing HO incorporate into the developing lesion in cartilage and bone and express chondrogenic and osteogenic transcription factors. Additionally, BCSPs isolated from developing HO similarly incorporate into new HO lesions upon transplantation. Finally, adventitial cells, but not pericytes, appear to play a supportive role in HO formation. Our findings indicate that BCSPs contribute to de novo bone formation during adulthood and may hold substantial regenerative potential. This article is protected by copyright. All rights reserved.

Sandberg, Y., A. W. Langerak, et al. "[Isolation and Characterization of Multipotent Precursor Cells from Murine Adipose Tissue using a Clinically Approved Cell Separation System]." Ned Tijdschr Geneeskd. 2016;160(0):A9866.

INTRODUCTION: Recent studies underscored the clinical potential of adipose-derived multipotent stem-/precursor cells (ASPCs). One of the main hurdles en route to clinical application was to isolate cells without having to perform expansion cultures outside the OR. A new generation of clinically approved, commercially available cell separation systems claims to provide ASPCs ready for application without further expansion cultures. However, it is unclear if the new systems yield sufficient cells of adequate quality for the use in autologous murine models. The aim of this study was to isolate and characterize adipose-derived precursor cells taken from the inguinal fat pat of wistar rats using InGeneron's clinically approved ARC-cell separation system. MATERIALS AND METHODS: We isolated cells from the inguinal fat pad of 3 male Wistar rats according to the manufacturer's protocol. In order to reduce the influence of the atmospheric oxygen on the multipotent precursor cells, one half of the cell suspension was cultivated under hypoxia (2% O2) simulating physiological conditions for ASPCs. As a control, the other half of the cells were cultivated under normoxia (21% O2). Cell surface markers CD90, CD29, CD45 and CD11b/c were analyzed by FACS, and osteogenic and adipogenic differentiation of the ASPCs was performed. Finally, cellular growth characteristics were assessed by evaluation of the cumulative population doublings and CFU assay, and metabolic activity was evaluated by WST-1 assay. RESULTS: Processing time was 90 (+/- 12) min. 1 g of adipose tissue yielded approximately 60 000 plastic

adhering cells. Both groups showed a high expression of the mesenchymal stem cell markers CD90 and CD29 while they were negative for the leucocyte markers CD45 and CD11b/c. A strong osteogenic differentiation and a sufficient adipogenic differentiation potential was proven for all ASPCs. Under hypoxia, ASPCs showed increased proliferation characteristics and CFU efficiency as well as a significantly increased metabolic activity. CONCLUSION: This study showed that sufficient multipotent ASPCs of appropriate quality can be isolated from the inguinal fat pad of Wistar rats using the ARC-cell separation system. As shown in previous studies, cultivation of cells under hypoxic conditions increased their stemness. Our findings will enable future studies that focus on autologous transplantation of ASPCs in a rat model, which most closely resembles a possible clinical application.

Sudo, T., T. Yokota, et al. "Endothelial Cell-Selective Adhesion Molecule Expression in Hematopoietic Stem/Progenitor Cells Is Essential for Erythropoiesis Recovery after Bone Marrow Injury." PLoS One. 2016 Apr 25;11(4):e0154189. doi: 10.1371/journal.pone.0154189. eCollection 2016.

Numerous red blood cells are generated every second from proliferative progenitor cells under a homeostatic state. Increased erythropoietic activity is required after myelo-suppression as a result of chemo-radio therapies. Our previous study revealed that the endothelial cell-selective adhesion molecule (ESAM), an authentic hematopoietic stem cell marker, plays essential roles in stress-induced hematopoiesis. To determine the physiological importance of ESAM in erythroid recovery, ESAM-knockout (KO) mice were treated with the anti-cancer drug, 5-fluorouracil (5-FU). ESAM-KO mice experienced severe and prolonged anemia after 5-FU treatment compared to wild-type (WT) mice. Eight days after the 5-FU injection, compared to WT mice, ESAM-KO mice showed reduced numbers of erythroid progenitors in bone marrow (BM) and spleen, and reticulocytes in peripheral blood. Megakaryocyte-erythrocyte progenitors (MEPs) from the BM of 5-FU-treated ESAM-KO mice showed reduced burst forming unit-erythrocyte (BFU-E) capacities than those from WT mice. BM transplantation revealed that hematopoietic stem/progenitor cells from ESAM-KO donors were more sensitive to 5-FU treatment than that from WT donors in the WT host mice. However, hematopoietic cells from WT donors transplanted into ESAM-KO host mice could normally reconstitute the erythroid lineage after a BM injury. These results suggested that ESAM expression in hematopoietic cells, but not environmental cells, is critical for hematopoietic recovery. We also found that 5-FU treatment induces the up-regulation of ESAM in primitive erythroid progenitors and macrophages that do not express ESAM under homeostatic conditions. The phenotypic change seen in macrophages might be functionally involved in the interaction between erythroid progenitors and their niche components during stress-induced acute erythropoiesis. Microarray analyses of primitive erythroid progenitors from 5-FU-treated WT and ESAM-KO mice revealed that various signaling pathways, including the GATA1 system, were impaired in ESAM-KO mice. Thus, our data demonstrate that ESAM expression in hematopoietic progenitors is essential for erythroid recovery after a BM injury.

Thakkar, U. G., A. V. Vanikar, et al. "Infusion of autologous adipose tissue derived neuronal differentiated mesenchymal stem cells and hematopoietic stem cells in post-traumatic paraplegia offers a viable therapeutic approach." Adv Biomed Res. 2016 Mar 16;5:51. doi: 10.4103/2277-9175.178792. eCollection 2016.

BACKGROUND: Spinal cord injury (SCI) is not likely to recover by current therapeutic modalities. Stem cell (SC) therapy (SCT) has promising results in regenerative medicine. We present our experience of co-infusion of autologous adipose tissue derived mesenchymal SC differentiated neuronal cells (N-Ad-MSC) and hematopoietic SCs (HSCs) in a set of patients with posttraumatic paraplegia. MATERIALS AND METHODS: Ten patients with posttraumatic paraplegia of mean age 3.42 years were volunteered for SCT. Their mean age was 28 years, and they had variable associated complications. They were subjected to adipose tissue resection for in vitro generation of N-Ad-MSC and bone marrow aspiration for generation of HSC. Generated SCs were infused into the cerebrospinal fluid (CSF) below injury site in all patients. RESULTS: Total mean quantum of SC infused was 4.04 ml with a mean nucleated cell count of 4.5 x 10(4)/muL and mean CD34+ of 0.35%, CD45-/90+ and CD45-/73+ of 41.4%, and 10.04%, respectively. All of them expressed transcription factors beta-3 tubulin and glial fibrillary acid protein. No untoward effect of SCT was noted. Variable and sustained improvement in Hauser's index and American Spinal Injury Association score was noted in all patients over a mean follow-up of 2.95 years. Mean injury duration was 3.42 years against the period of approximately 1-year required for natural recovery, suggesting a positive role of SCs. CONCLUSION: Co-infusion of N-Ad-MSC and HSC in CSF is safe and viable therapeutic approach for SCIs.

Verran, J. A. and P. J. Reid "Replicated testing of the Nursing Technology Model." Nurs Res. 1987 May-Jun;36(3):190-4.

The purpose of this study was to replicate the testing of a model to explain complexity of nursing care in the ambulatory care setting. The Nursing Technology Model (Verran & Shaw, 1986) has as its theoretical base a sociological perspective of organizational analysis in which technology is viewed as the antecedent to organizational structure. The model includes materials technology as the nature of the ambulatory care client and knowledge technology as the principal type of activities pertinent to nursing care delivery. The characteristics of these technology types were organized into causal paths to explain complexity of care. Two ambulatory care sites were sampled to obtain a client sample of 610 rating sets. Results were essentially similar to earlier research with R2s for complexity indexes at the same level of .34. Only one regression equation evidenced instability in regression coefficients and the R2. Analysis of findings indicated that other variables, such as some aspects of structure, may need to be further specified in the model in order to increase its explanatory power.

Yamamoto, H. "Runx1 downregulates stem cell/megakaryocytic transcription programs that support niche interactions." Rinsho Ketsueki. 2016;57(3):278-87. doi: 10.11406/rinketsu.57.278.

Disrupting mutations of theRUNX1gene are found in 10% of Myelodysplasia (MDS) and 30% of Acute Myeloid Leukemia (AML) patients. Previous studies have revealed an increase in hematopoietic stem and multipotent progenitor cells (HSC/MPP) in conditionalRunx1knockout (KO) mice - but the molecular mechanism is unresolved. We investigated the myeloid progenitor (MP) compartment in KO mice, arguing that disruptions at the HSC/MPP level may be amplified in downstream cells. We demonstrate that the MP compartment is increased by >5-fold inRunx1KO mice, with a prominent skewing towards Megakaryocyte (Meg) progenitors. Runx1-deficient Granulocyte-Macrophage Progenitors (GMPs) are characterized by increased cloning capacity, impaired development into mature cells, and HSC and Meg transcription signatures. A HSC/MPP subpopulation expressing Meg markers was also increased in Runx1-deficient mice. Rescue experiments coupled with transcriptome analysis and Runx1 DNA-binding assays demonstrated that lineage separation between Meg and GM commitment is marked by Runx1 suppression of genes encoding adherence and motility proteins (Tek, Jam3, Plxnc1, Pcdh7, and Selp) that support HSC/Meg interactions with the BM niche.In vitroassays confirmed that enforced Tek expression in HSC/MPP increases Meg output. Interestingly, besides this key repressor function of Runx1 to control lineage decisions and cell numbers in progenitors, our study also revealed a critical activating function in erythroblast differentiation, in addition to its known importance in Meg and G/M maturation. Thus both repressor and activator functions of Runx1 at multiple hematopoietic stages and lineages likely contribute to the tumor suppressor activity in MDS and AML.

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