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Stem Cell

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New York Stem Cell 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; technology; 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.

Adamson, J. W. (1997). "Cord blood stem cell banking and transplantation." Stem Cells **15 Suppl 1**: 57-59; discussion 59-61.

Cord blood banking for the purpose of stem cell transplantation is a rapidly growing area of medical interest. Based on the fact that cord blood contains large numbers of stem and progenitor cells, transplantation of cord blood for marrow reconstitution was first attempted in 1988. The success of this initial transplant between related donor and patient rapidly led to the establishment of efforts to collect, store and eventually transplant unrelated cord blood samples. A collection and storage program established by the New York Blood Center has led to more than 400 such transplants. The results demonstrate acceptable rates of engraftment and little graft-versus-host disease compared to the results employing adult marrow. As a consequence of these observations, considerable effort is being made to establish cord blood banks around the world.

Ban, D. X., et al. (2011). "Combination of activated Schwann cells with bone mesenchymal stem cells: the best cell strategy for repair after spinal cord injury in rats." Regen Med **6**(6): 707-720.

AIM: We aim to explore the repair effect of combined cell therapy using activated Schwann cells (ASCs) and bone mesenchymal stem cells (BMSCs) in traumatic spinal cord injury (SCI) in rats. MATERIALS & METHODS: ASCs and BMSCs were used for combined transplantation to treat acute SCI in rats, both of which can be obtained from SCI patients. ASCs were obtained by prior ligation of saphenous nerve and BMSCs by flush of the marrow cavity with Dulbecco's modified Eagle's medium solution. Our experiment in vitro confirmed that ASCs promoted BMSCs to differentiate into mature neural cells. It also indicates that BMSCs hold the potential to repair CNS injury. ASCs and BMSCs were co-transplanted into the injured epicenter of spinal cord made by the New York University (NYU) impactor machine using a 10 g x 50 mm drop weight. Complete ASCs, BMSCs and Dulbecco's modified Eagle's medium were also transplanted in rats with SCI as a control. Recovery of rat's hindlimb function was serially evaluated by Basso, Beattie, Bresnahan locomotor rating scale and footprint analysis. Changes of neurological potential were recorded by nerve electrophysiologic test. Improvement in the microenvironment of the injured

spinal cord was evaluated by hematoxylin and eosin staining, glial fibrillary acidic protein staining, biotinylated dextran amine anterograde tracing and electron microscopy. RESULTS: Using biotinylated dextran amine anterograde tracing, we demonstrated that there were more regenerative axons of corticospinal tract surrounding and passing through the injured cavity to the caudal cord in the ASC-BMSC co-graft group than those in the other three groups, and we also confirmed this further by quantitative analysis. Immunostaining for glial fibrillary acidic protein showed the smallest population of astrocytes in the injury epicenter in the ASC-BMSC group compared with the other three groups. Relatively complete myelin sheaths and organelles were found in the ASC-BMSC group compared with the other three groups under electron microscopy. CONCLUSION: Effective co-transplantation of ASCs and BMSCs promotes functional recovery in rats' hindlimbs and reduces the formation of glial scar, and remyelinates the injured axons as compared with the other three groups. This conclusion was also supported by the observation of immunohistochemistry staining and electron microscopy, suggesting the possible clinical application for the treatment of spinal injury.

Barker, J. N., et al. (2010). "Availability of cord blood extends allogeneic hematopoietic stem cell transplant access to racial and ethnic minorities." Biol Blood Marrow Transplant **16**(11): 1541-1548.

Allogeneic transplant access can be severely limited for patients of racial and ethnic minorities without suitable sibling donors. Whether cord blood (CB) transplantation can extend transplant access because of the reduced stringency of required HLA-match is not proven. We prospectively evaluated availability of unrelated donors (URD) and CB according to patient ancestry in 553 patients without suitable sibling donors. URDs had priority if adequate donors were available. Otherwise >/=4/6 HLA-matched CB grafts were chosen utilizing double units to augment graft dose. Patients had highly diverse ancestries including 35% non-Europeans. In 525 patients undergoing combined searches, 10/10 HLA-matched URDs were identified in 53% of those with European ancestry, but only 21% of patients with non-European origins (P < .001). However, the majority of both groups had 5-6/6 CB units. The 269 URD transplant recipients were predominantly European, with non-European patients accounting for only 23%. By contrast, 56% of CB transplant recipients had non-European ancestries (P < .001). Of 26 patients without any suitable stem cell source, 73% had non-European ancestries (P < .001). Their median weight was significantly higher than CB transplant recipients (P <.001), partially accounting for their lack of a CB graft. Availability of CB significantly extends allo-transplant access, especially in non-European patients, and has the greatest potential to provide a suitable stem cell source regardless of race or ethnicity. Minority patients in need of allografts, but without suitable matched sibling donors, should be referred for combined URD and CB searches to optimize transplant access.

Barriga, F. and M. A. Wietstruck (2007). "Search for unrelated donor umbilical cord blood units for allogeneic stem cell transplantation: results in two time periods." Transplant Proc **39**(3): 629-630.

UNLABELLED: Umbilical cord blood (UCB) banks have increased their stock worldwide in the past years. There are more than 230,000 available units today. The ideal UCB graft is a unit that is matched in five or six of six HLA. A, B (low-resolution) and DRB1 (high-resolution) alleles and which has over 2.5 x 107 nucleated cells/kg body weight (BW). Four of six matched units are also used specially if the cell dose gives more than 3 x 10(7) nucleated cells/kg BW. Our unrelated donor UCB transplant program was started in 1996 searching international cord blood banks (Netcord, New York) for patients with a definitive or potential indication for stem cell transplantation who lacked a matched family donor. PATIENTS AND METHODS: From 1995 to 1996, a search was initiated for 87 patients with malignant (n = 56, 37 acute leukemia) and nonmalignant conditions (16 congenital diseases, 14 aplastic anemia). Patient data along with low-resolution A, B, and DR typing were sent to the New York Blood Center, along with a blood sample for high-resolution DRB1 typing. Parallel searches were done in the Netcord database among UCB units with reported high-resolution DRB1 typing. Forty-eight searches were done between 1995 and 2000 (31 with high resolution) and 39 were done between 2000 and 2005 (33 with high resolution). UCB units were considered adequate if they had more than 2.7 x 10(7) cells/kg BW. RESULTS: During the first period, four patients (13%) matched five of six high-resolution unit and 21 (67%) a four of six match. During the second period, 15 patients (46%) found a five of six match and 16 (48%) a four of six match (P = .012). CONCLUSION: Nearly half of our patients find an optimal matched UCB unit for transplantation in international banks. The creation of a local UCB bank in our country is supported by these data.

Bartunek, J., et al. (2013). "Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failURE) multicenter randomized trial with lineage-specified biologics." J Am Coll Cardiol **61**(23): 2329-2338.

OBJECTIVES: This study sought to evaluate the feasibility and safety of autologous bone marrow-

derived and cardiogenically oriented mesenchymal stem cell therapy and to probe for signs of efficacy in patients with chronic heart failure. BACKGROUND: In pre-clinical heart failure models, cardiopoietic stem cell therapy improves left ventricular function and blunts pathological remodeling. METHODS: The C-CURE (Cardiopoietic stem Cell therapy in heart failURE) trial, a prospective, multicenter, randomized trial, was conducted in patients with heart failure of ischemic origin who received standard of care or standard of care plus lineage-specified stem cells. In the cell therapy arm, bone marrow was harvested and isolated mesenchymal stem cells were exposed to a cardiogenic cocktail. Derived cardiopoietic stem cells, meeting release criteria under Good Manufacturing Practice, were delivered by endomyocardial injections guided by left ventricular electromechanical mapping. Data acquisition and analysis were performed in blinded fashion. The primary endpoint was feasibility/safety at 2-year follow-up. Secondary endpoints included cardiac structure/function and measures of global clinical performance 6 months post-therapy. RESULTS: Mesenchymal stem cell cocktail-based priming was achieved for each patient with the dose attained in 75% and delivery without complications in 100% of cases. There was no evidence of increased cardiac or systemic toxicity induced by cardiopoietic cell therapy. Left ventricular ejection fraction was improved by cell therapy (from 27.5 +/- 1.0% to 34.5 +/- 1.1%) versus standard of care alone (from 27.8 +/- 2.0% to 28.0 +/- 1.8%, $p < 0.0001$) and was associated with a reduction in left ventricular end-systolic volume (-24.8 +/- 3.0 ml vs. -8.8 +/- 3.9 ml, $p < 0.001$). Cell therapy also improved the 6-min walk distance (+62 +/- 18 m vs. -15 +/- 20 m, $p < 0.01$) and provided a superior composite clinical score encompassing cardiac parameters in tandem with New York Heart Association functional class, quality of life, physical performance, hospitalization, and event-free survival. CONCLUSIONS: The C-CURE trial implements the paradigm of lineage guidance in cell therapy. Cardiopoietic stem cell therapy was found feasible and safe with signs of benefit in chronic heart failure, meriting definitive clinical evaluation. (C-Cure Clinical Trial; NCT00810238).

Baylis, F. (2009). "For love or money? The saga of Korean women who provided eggs for embryonic stem cell research." Theor Med Bioeth **30**(5): 385-396.

In 2004 and 2005, Woo-Suk Hwang achieved international stardom with publications in Science reporting on successful research involving the creation of stem cells from cloned human embryos. The wonder and success all began to unravel, however, when serious ethical concerns were raised about the source of the eggs for this research. When the egg scandal had completely unfolded, it turned out that many of the women who provided eggs for stem cell research had not provided valid consents and that nearly 75% of the women egg providers had received cash or in-kind payments. Among those who did not receive direct benefits, some cited patriotism as their reason for participating in embryonic stem cell research, hence the question "for love or money?"--namely, patriotism versus payment. This paper summarizes the Hwang debacle with particular attention to the egg scandal and ends with some preliminary thoughts on patriotism as a motive for research participation.

Bhawnani, N., et al. (2021). "Effectiveness of Stem Cell Therapies in Improving Clinical Outcomes in Patients With Heart Failure." Cureus **13**(8): e17236.

Heart failure (HF), continuing to be a notable cause of morbidity and mortality worldwide, also is a noteworthy economic burden to the patients. Current medical management of HF has poor efficacy to completely arrest or reverse the progression to end-stage disease. As the option of cardiac transplantation remains limited to few patients, the stem cell approach continues to be a promising one in developing a novel therapy in the treatment of HF. This review attempts to discuss and compare the outcomes of numerous clinical trials that involved treatment of HF of variable etiologies with stem cells of numerous lineages such as bone marrow-derived cells (BMCs), mesenchymal stem cells (MSCs), cardiosphere derived progenitor cells (CDCs), etc. We reviewed articles and randomized controlled trials (RCT) that used stem cells to treat heart failure. The articles and RCT studies were obtained through a search on PubMed and Medline databases and performed using regular and medical subject heading (MeSH) keyword search strategy. A total of 17 trial-based studies, along with other articles that met the aim of the review, were selected. A discussion of the findings from major clinical trials such as the C-CURE, CHART-1, POSEIDON, POSEIDON-DCM, TAC-HFT, and other small scale trials highlights the change in functional and mechanical parameters of HF, namely, left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), end-systolic volume (ESV), 6-minute walking test distance (6MWTD), N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and assessment of New York heart association (NYHA) class of heart failure, and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score to reflect improvement in quality of life (QoL) of patients. Out of the studies analyzed, the majority reported significant improvements in at least two of the parameters mentioned above. However, more phase three randomized trials are required to compare the efficacy of multiple lineages of stem cells,

factoring in molecular and dosage factors to develop a standardized therapy.

da Rocha Loures, D. R., et al. (2010). "Bone marrow stem cell transplantation and coronary artery bypass grafting surgery for chronic ischemic myocardiopathy." Heart Surg Forum **13**(3): E161-164.

We studied 12 consecutive patients with chronic ischemic myocardiopathy treated with bone marrow adult stem cell (ASC) transplantation and coronary artery bypass grafting (CABG). The aim of the study was to evaluate functional class (New York Heart Association), wall motion score index (WMSI), and ejection fraction by echocardiography and to evaluate myocardial perfusion by single-photon emission computed tomography (SPECT). Follow-up evaluations were performed at 3, 6, and 12 months. The results revealed functional class improvement until 12 months, a progressive increase in the ejection fraction of 15% to 20% in the first 6 months, and a progressive increase in the WMSI by 35% to 45% in 12 months. Evaluation of the WMSI in the stem cell and CABG areas separately revealed a similar improvement in the first 3 months and a better progression in the CABG area. SPECT images revealed perfusion improvements in ischemic areas and no difference in fibrous tissue areas. These preliminary results show the safety of the method and its reproducibility. When performed concomitantly with CABG, bone marrow ASC transplantation may improve functional class, ejection fraction, WMSI, and myocardial perfusion. This study will be completed with all patients followed up for 12 months and compared with a control group.

Dahan, J. F. and C. F. Auerbach (2006). "A qualitative study of the trauma and posttraumatic growth of multiple myeloma patients treated with peripheral blood stem cell transplant." Palliat Support Care **4**(4): 365-387.

OBJECTIVE: The study was conducted to understand the emotional impact of multiple myeloma, as well as the impact of its principle treatment, peripheral blood stem cell transplant (PBSCT). The absence of psycho-oncology research literature on this population prompted the need for a hypothesis-generating investigation. Thus, a qualitative design was used to construct a theoretical model of the trauma relating to diagnosis and treatment of myeloma. The study also incorporates the important period of reflection and growth following treatment. METHODS: The sample consisted of 3 women and 3 men treated for myeloma at a New York City-based cancer treatment center. Data from individual interviews were audiotaped and transcribed. After extensive review, the data were categorized into groups of repeating ideas, themes and broad theoretical constructs. RESULTS: A five-construct model emerged from the data analysis that integrated a model of trauma and growth presented in earlier work (Auerbach et al., 2006). These constructs roughly correspond with stages of illness, but do not necessarily imply a linear process, as suggested by stage models. The first construct is diagnosis. Patients receive the news that they have multiple myeloma. Initial reactions are discussed and a treatment plan takes form. In the second construct, treatment, patients highlight the physical and emotional hurdles confronted throughout treatment. The third construct, network of safety, presents social factors that play a role in comforting patients throughout illness. Patients recognize the importance of a strong support system during their experiences. In the fourth construct, recuperation, physical energy is regained after an arduous recovery period. This contributes to higher spirits and a motivation to reengage with life. The fifth construct is reflection and new existence. Patients strive to balance a new reality that relapse and death are inevitable, along with their need to live a meaningful life. Many do not yet appreciate how their disease has impacted them, but describe how their interpersonal lives and perceptions have changed, both positively and negatively. SIGNIFICANCE OF RESULTS: Limitations of the study, future directions for research and clinical implications are discussed.

Diaz-Navarro, R., et al. (2021). "Stem cell therapy for dilated cardiomyopathy." Cochrane Database Syst Rev **7**: CD013433.

BACKGROUND: Stem cell therapy (SCT) has been proposed as an alternative treatment for dilated cardiomyopathy (DCM), nonetheless its effectiveness remains debatable. OBJECTIVES: To assess the effectiveness and safety of SCT in adults with non-ischaemic DCM. SEARCH METHODS: We searched CENTRAL in the Cochrane Library, MEDLINE, and Embase for relevant trials in November 2020. We also searched two clinical trials registers in May 2020. SELECTION CRITERIA: Eligible studies were randomized controlled trials (RCT) comparing stem/progenitor cells with no cells in adults with non-ischaemic DCM. We included co-interventions such as the administration of stem cell mobilizing agents. Studies were classified and analysed into three categories according to the comparison intervention, which consisted of no intervention/placebo, cell mobilization with cytokines, or a different mode of SCT. The first two comparisons (no cells in the control group) served to assess the efficacy of SCT while the third (different mode of SCT) served to complement the review with information about safety and other information of potential utility for a better understanding of the effects of SCT. DATA COLLECTION AND ANALYSIS: Two review

authors independently screened all references for eligibility, assessed trial quality, and extracted data. We undertook a quantitative evaluation of data using random-effects meta-analyses. We evaluated heterogeneity using the I(2) statistic. We could not explore potential effect modifiers through subgroup analyses as they were deemed uninformative due to the scarce number of trials available. We assessed the certainty of the evidence using the GRADE approach. We created summary of findings tables using GRADEpro GDT. We focused our summary of findings on all-cause mortality, safety, health-related quality of life (HRQoL), performance status, and major adverse cardiovascular events. MAIN RESULTS: We included 13 RCTs involving 762 participants (452 cell therapy and 310 controls). Only one study was at low risk of bias in all domains. There were many shortcomings in the publications that did not allow a precise assessment of the risk of bias in many domains. Due to the nature of the intervention, the main source of potential bias was lack of blinding of participants (performance bias). Frequently, the format of the continuous data available was not ideal for use in the meta-analysis and forced us to seek strategies for transforming data in a usable format. We are uncertain whether SCT reduces all-cause mortality in people with DCM compared to no intervention/placebo (mean follow-up 12 months) (risk ratio (RR) 0.84, 95% confidence interval (CI) 0.54 to 1.31; I(2) = 0%; studies = 7, participants = 361; very low-certainty evidence). We are uncertain whether SCT increases the risk of procedural complications associated with cells injection in people with DCM (data could not be pooled; studies = 7; participants = 361; very low-certainty evidence). We are uncertain whether SCT improves HRQoL (standardized mean difference (SMD) 0.62, 95% CI 0.01 to 1.23; I(2) = 72%; studies = 5, participants = 272; very low-certainty evidence) and functional capacity (6-minute walk test) (mean difference (MD) 70.12 m, 95% CI -5.28 to 145.51; I(2) = 87%; studies = 5, participants = 230; very low-certainty evidence). SCT may result in a slight functional class (New York Heart Association) improvement (data could not be pooled; studies = 6, participants = 398; low-certainty evidence). None of the included studies reported major adverse cardiovascular events as defined in our protocol. SCT may not increase the risk of ventricular arrhythmia (data could not be pooled; studies = 8, participants = 504; low-certainty evidence). When comparing SCT to cell mobilization with granulocyte-colony stimulating factor (G-CSF), we are uncertain whether SCT reduces all-cause mortality (RR 0.46, 95% CI 0.16 to 1.31; I(2) = 39%; studies = 3, participants = 195; very low-certainty evidence). We are uncertain whether SCT increases the risk of procedural complications associated with cells injection (studies = 1, participants = 60; very low-certainty evidence). SCT may not improve HRQoL (MD 4.61 points, 95% CI -5.62 to 14.83; studies = 1, participants = 22; low-certainty evidence). SCT may improve functional capacity (6-minute walk test) (MD 140.14 m, 95% CI 119.51 to 160.77; I(2) = 0%; studies = 2, participants = 155; low-certainty evidence). None of the included studies reported MACE as defined in our protocol or ventricular arrhythmia. The most commonly reported outcomes across studies were based on physiological measures of cardiac function where there were some beneficial effects suggesting potential benefits of SCT in people with non-ischaemic DCM. However, it is unclear if this intermediate effects translates into clinical benefits for these patients. With regard to specific aspects related to the modality of cell therapy and its delivery, uncertainties remain as subgroup analyses could not be performed as planned, making it necessary to wait for the publication of several studies that are currently in progress before any firm conclusion can be reached. AUTHORS' CONCLUSIONS: We are uncertain whether SCT in people with DCM reduces the risk of all-cause mortality and procedural complications, improves HRQoL, and performance status (exercise capacity). SCT may improve functional class (NYHA), compared to usual care (no cells). Similarly, when compared to G-CSF, we are also uncertain whether SCT in people with DCM reduces the risk of all-cause mortality although some studies within this comparison observed a favourable effect that should be interpreted with caution. SCT may not improve HRQoL but may improve to some extent performance status (exercise capacity). Very low-quality evidence reflects uncertainty regarding procedural complications. These suggested beneficial effects of SCT, although uncertain due to the very low certainty of the evidence, are accompanied by favourable effects on some physiological measures of cardiac function. Presently, the most effective mode of administration of SCT and the population that could benefit the most is unclear. Therefore, it seems reasonable that use of SCT in people with DCM is limited to clinical research settings. Results of ongoing studies are likely to modify these conclusions.

Domae, K., et al. (2021). "Clinical Outcomes of Autologous Stem Cell-Patch Implantation for Patients With Heart Failure With Nonischemic Dilated Cardiomyopathy." J Am Heart Assoc **10**(13): e008649.

Background Clinical effectiveness of autologous skeletal cell-patch implantation for nonischemic dilated cardiomyopathy has not been clearly elucidated in clinical settings. This clinical study aimed to determine the feasibility, safety,

therapeutic efficacy, and the predictor of responders of this treatment in patients with nonischemic dilated cardiomyopathy. Methods and Results Twenty-four nonischemic dilated cardiomyopathy patients with left ventricular ejection fraction <35% on optimal medical therapy were enrolled. Autologous cell patches were implanted over the surface of the left ventricle through left minithoracotomy without procedure-related complications and lethal arrhythmia. We identified 13 responders and 11 nonresponders using the combined indicator of a major cardiac adverse event and incidence of heart failure event. In the responders, symptoms, exercise capacity, and cardiac performance were improved postoperatively (New York Heart Association class II 7 [54%] and III 6 [46%] to New York Heart Association class II 12 [92%] and I 1 [8%], P<0.05, 6-minute walk test; 471 m [370-541 m] to 525 m [425-555 m], P<0.05, left ventricular stroke work index; 31.1 g.m(2).beat [22.7-35.5 g.m(2).beat] to 32.8 g.m(2).beat [28-38.5 g.m(2).beat], P=0.21). However, such improvement was not observed in the nonresponders. In responders, the actuarial survival rate was 90.9+/-8.7% at 5 years, which was superior to the estimated survival rate of 70.9+/-5.4% using the Seattle Heart Failure Model. However, they were similar in nonresponders (47.7+/-21.6% and 56.3+/-8.1%, respectively). Multivariate regression model with B-type natriuretic peptide, pulmonary capillary wedge pressure, and expression of histone H3K4me3 (H3 lysine 4 trimethylation) strongly predicted the responder of this treatment (B-type natriuretic peptide: odds ratio [OR], 0.96; pulmonary capillary wedge pressure: OR, 0.58; H3K4me3: OR, 1.35, receiver operating characteristic-area under the curve, 0.96, P<0.001). Conclusions This clinical trial demonstrated that autologous skeletal stem cell-patch implantation might promise functional recovery and good clinical outcome in selected patients with nonischemic dilated cardiomyopathy, in addition to safety and feasibility. Registration URL: http://www.umin.ac.jp/english/. Unique identifiers: UMIN000003273, UMIN0000012906 and UMIN000015892.

Eapen, M., et al. (2010). "Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis." Lancet Oncol **11**(7): 653-660.

BACKGROUND: Umbilical-cord blood (UCB) is increasingly considered as an alternative to peripheral blood progenitor cells (PBPCs) or bone marrow, especially when an HLA-matched adult unrelated donor is not available. We aimed to determine the optimal role of UCB grafts in transplantation for adults with acute leukaemia, and to establish whether current graft-selection practices are appropriate. METHODS: We used Cox regression to retrospectively compare leukaemia-free survival and other outcomes for UCB, PBPC, and bone marrow transplantation in patients aged 16 years or over who underwent a transplant for acute leukaemia. Data were available on 1525 patients transplanted between 2002 and 2006. 165 received UCB, 888 received PBPCs, and 472 received bone marrow. UCB units were matched at HLA-A and HLA-B at antigen level, and HLA-DRB1 at allele level (n=10), or mismatched at one (n=40) or two (n=115) antigens. PBPCs and bone-marrow grafts from unrelated adult donors were matched for allele-level HLA-A, HLA-B, HLA-C, and HLA-DRB1 (n=632 and n=332, respectively), or mismatched at one locus (n=256 and n=140, respectively). FINDINGS: Leukaemia-free survival in patients after UCB transplantation was comparable with that after 8/8 and 7/8 allele-matched PBPC or bone-marrow transplantation. However, transplant-related mortality was higher after UCB transplantation than after 8/8 allele-matched PBPC recipients (HR 1.62, 95% CI 1.18-2.23; p=0.003) or bone-marrow transplantation (HR 1.69, 95% CI 1.19-2.39; p=0.003). Grades 2-4 acute and chronic graft-versus-host disease (GvHD) were lower in UCB recipients compared with allele-matched PBPC (HR 0.57, 95% 0.42-0.77; p=0.002 and HR 0.38, 0.27-0.53; p=0.003, respectively), while the incidence of chronic, but not acute GvHD, was lower after UCB than after 8/8 allele-matched bone-marrow transplantation (HR 0.63, 0.44-0.90; p=0.01). INTERPRETATION: These data support the use of UCB for adults with acute leukaemia when there is no HLA-matched unrelated adult donor available, and when a transplant is needed urgently.

Fan, M., et al. (2019). "Efficacy of mesenchymal stem cell therapy in systolic heart failure: a systematic review and meta-analysis." Stem Cell Res Ther **10**(1): 150.

BACKGROUND: Heart failure (HF) is the end stage of most heart disease. Mesenchymal stem cells (MSCs), with their specific biological effects, have been applied in several clinical trials to evaluate the efficacy in HF therapy. We performed this meta-analysis to review the clinical evidence of their therapeutic effect on HF. METHODS: Three databases were searched. The outcomes of interest were death, readmission, the 6-min walk test (6MWT), New York Heart Association (NYHA) class and left ventricular ejection fraction (LVEF). The relative risk (RR) and weighted mean difference (WMD) were calculated to evaluate the effects of MSCs on HF compared to placebo. RESULTS: A total of nine studies were included, involving 612 patients who underwent MSCs or placebo treatment. The overall rate of death showed a trend of reduction of 36% (RR [CI] = 0.64 [0.35, 1.16], p = 0.143) in the MSC treatment group. The

incidence of readmission was reduced by 34% (RR [CI] = 0.66 [0.51, 0.85], p = 0.001). The patients in the MSC treatment group realised an average of 40.44 m (WMD [95% CI] = 40.44 m [19.07, 61.82], p < 0.0001) improvement in 6MWT. The NYHA class was reduced obviously in the MSC group (WMD [95% CI] = - 0.42 [- 0.64, - 0.20], p < 0.0001). The changes of LVEF from baseline were significantly more than 5.25% (WMD [95% CI] = 5.25 [3.58, 6.92], p < 0.0001) in the MSCs group, unlike in the placebo group. CONCLUSIONS: Our results suggested that MSC treatment is an effective therapy for HF by improving the prognosis and exercise capacity. SCs derived from allosomes have superior therapeutic effects, and intracoronary injection is the optimum MSC delivery approach. Short-term cryopreservation is feasible in MSCs storage or transport.

Fisher, S. A., et al. (2014). "Stem cell therapy for chronic ischaemic heart disease and congestive heart failure." Cochrane Database Syst Rev(4): CD007888.

BACKGROUND: A promising approach to the treatment of chronic ischaemic heart disease (IHD) and heart failure is the use of stem cells. The last decade has seen a plethora of randomised controlled trials (RCTs) developed worldwide which have generated conflicting results. OBJECTIVES: The critical evaluation of clinical evidence on the safety and efficacy of autologous adult bone marrow-derived stem cells (BMSC) as a treatment for chronic ischaemic heart disease (IHD) and heart failure. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2013, Issue 3), MEDLINE (from 1950), EMBASE (from 1974), CINAHL (from 1982) and the Transfusion Evidence Library (from 1980), together with ongoing trial databases, for relevant trials up to 31st March 2013. SELECTION CRITERIA: Eligible studies included RCTs comparing autologous adult stem/progenitor cells with no autologous stem/progenitor cells in participants with chronic IHD and heart failure. Co-interventions such as primary angioplasty, surgery or administration of stem cell mobilising agents, were included where administered to treatment and control arms equally. DATA COLLECTION AND ANALYSIS: Two review authors independently screened all references for eligibility, assessed trial quality and extracted data. We undertook a quantitative evaluation of data using fixed-effect meta-analyses. We evaluated heterogeneity using the I(2) statistic; we explored considerable heterogeneity (I(2) > 75%) using a random-effects model and subgroup analyses. MAIN RESULTS: We include 23 RCTs involving 1255 participants in this review. Risk of bias was generally low, with the majority of studies reporting appropriate methods of randomisation and blinding, Autologous bone marrow stem cell treatment reduced the incidence of mortality (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.14 to 0.53, P = 0.0001, 8 studies, 494 participants, low quality evidence) and rehospitalisation due to heart failure (RR 0.26, 95% CI 0.07 to 0.94, P = 0.04, 2 studies, 198 participants, low quality evidence) in the long term (>/=12 months). The treatment had no clear effect on mortality (RR 0.68, 95% CI 0.32 to 1.41, P = 0.30, 21 studies, 1138 participants, low quality evidence) or rehospitalisation due to heart failure (RR 0.36, 95% CI 0.12 to 1.06, P = 0.06, 4 studies, 236 participants, low quality evidence) in the short term (< 12 months), which is compatible with benefit, no difference or harm. The treatment was also associated with a reduction in left ventricular end systolic volume (LVESV) (mean difference (MD) -14.64 ml, 95% CI -20.88 ml to -8.39 ml, P < 0.00001, 3 studies, 153 participants, moderate quality evidence) and stroke volume index (MD 6.52, 95% CI 1.51 to 11.54, P = 0.01, 2 studies, 62 participants, moderate quality evidence), and an improvement in left ventricular ejection fraction (LVEF) (MD 2.62%, 95% CI 0.50% to 4.73%, P = 0.02, 6 studies, 254 participants, moderate quality evidence), all at long-term follow-up. Overall, we observed a reduction in functional class (New York Heart Association (NYHA) class) in favour of BMSC treatment during short-term follow-up (MD -0.63, 95% CI -1.08 to -0.19, P = 0.005, 11 studies, 486 participants, moderate quality evidence) and long-term follow-up (MD -0.91, 95% CI -1.38 to -0.44, P = 0.0002, 4 studies, 196 participants, moderate quality evidence), as well as a difference in Canadian Cardiovascular Society score in favour of BMSC (MD -0.81, 95% CI -1.55 to -0.07, P = 0.03, 8 studies, 379 participants, moderate quality evidence). Of 19 trials in which adverse events were reported, adverse events relating to the BMSC treatment or procedure occurred in only four individuals. No long-term adverse events were reported. Subgroup analyses conducted for outcomes such as LVEF and NYHA class revealed that (i) route of administration, (ii) baseline LVEF, (iii) cell type, and (iv) clinical condition are important factors that may influence treatment effect. AUTHORS' CONCLUSIONS: This systematic review and meta-analysis found moderate quality evidence that BMSC treatment improves LVEF. Unlike in trials where BMSC were administered following acute myocardial infarction (AMI), we found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart failure, although the quality of evidence was low.

Fisher, S. A., et al. (2016). "Stem cell therapy for chronic ischaemic heart disease and congestive heart failure." Cochrane Database Syst Rev **12**: CD007888.

BACKGROUND: A promising approach to the treatment of chronic ischaemic heart disease and congestive heart failure is the use of stem cells. The last decade has seen a plethora of randomised controlled trials developed worldwide, which have generated conflicting results. OBJECTIVES: The critical evaluation of clinical evidence on the safety and efficacy of autologous adult bone marrow-derived stem/progenitor cells as a treatment for chronic ischaemic heart disease and congestive heart failure. SEARCH METHODS: We searched CENTRAL in the Cochrane Library, MEDLINE, Embase, CINAHL, LILACS, and four ongoing trial databases for relevant trials up to 14 December 2015. SELECTION CRITERIA: Eligible studies were randomised controlled trials comparing autologous adult stem/progenitor cells with no cells in people with chronic ischaemic heart disease and congestive heart failure. We included co-interventions, such as primary angioplasty, surgery, or administration of stem cell mobilising agents, when administered to treatment and control arms equally. DATA COLLECTION AND ANALYSIS: Two review authors independently screened all references for eligibility, assessed trial quality, and extracted data. We undertook a quantitative evaluation of data using random-effects meta-analyses. We evaluated heterogeneity using the I(2) statistic and explored substantial heterogeneity (I(2) greater than 50%) through subgroup analyses. We assessed the quality of the evidence using the GRADE approach. We created a 'Summary of findings' table using GRADEprofiler (GRADEpro), excluding studies with a high or unclear risk of selection bias. We focused our summary of findings on long-term follow-up of mortality, morbidity outcomes, and left ventricular ejection fraction measured by magnetic resonance imaging. MAIN RESULTS: We included 38 randomised controlled trials involving 1907 participants (1114 cell therapy, 793 controls) in this review update. Twenty-three trials were at high or unclear risk of selection bias. Other sources of potential bias included lack of blinding of participants (12 trials) and full or partial commercial sponsorship (13 trials).Cell therapy reduced the incidence of long-term mortality (>/= 12 months) (risk ratio (RR) 0.42, 95% confidence interval (CI) 0.21 to 0.87; participants = 491; studies = 9; I(2) = 0%; low-quality evidence). Periprocedural adverse events associated with the mapping or cell/placebo injection procedure were infrequent. Cell therapy was also associated with a long-term reduction in the incidence of non-fatal myocardial infarction (RR 0.38, 95% CI 0.15 to 0.97; participants = 345; studies = 5; I(2) = 0%; low-quality evidence) and incidence of arrhythmias (RR 0.42, 95% CI 0.18 to 0.99; participants = 82; studies = 1; low-quality evidence). However, we found no evidence that cell therapy affects the risk of rehospitalisation for heart failure (RR 0.63, 95% CI 0.36 to 1.09; participants = 375; studies = 6; I(2) = 0%; low-quality evidence) or composite incidence of mortality, non-fatal myocardial infarction, and/or rehospitalisation for heart failure (RR 0.64, 95% CI 0.38 to 1.08; participants = 141; studies = 3; I(2) = 0%; low-quality evidence), or long-term left ventricular ejection fraction when measured by magnetic resonance imaging (mean difference -1.60, 95% CI -8.70 to 5.50; participants = 25; studies = 1; low-quality evidence). AUTHORS' CONCLUSIONS: This systematic review and meta-analysis found low-quality evidence that treatment with bone marrow-derived stem/progenitor cells reduces mortality and improves left ventricular ejection fraction over short- and long-term follow-up and may reduce the incidence of non-fatal myocardial infarction and improve New York Heart Association (NYHA) Functional Classification in people with chronic ischaemic heart disease and congestive heart failure. These findings should be interpreted with caution, as event rates were generally low, leading to a lack of precision.

Florea, V., et al. (2020). "The impact of patient sex on the response to intramyocardial mesenchymal stem cell administration in patients with non-ischaemic dilated cardiomyopathy." Cardiovasc Res **116**(13): 2131-2141.

AIMS: Sex differences impact the occurrence, presentation, prognosis, and response to therapy in heart disease. Particularly, the phenotypic presentation of patients with non-ischaemic dilated cardiomyopathy (NIDCM) differs between men and women. However, whether the response to mesenchymal stem cell (MSC) therapy is influenced by sex remains unknown. We hypothesize that males and females with NIDCM respond similarly to MSC therapy. METHODS AND RESULTS: Male (n = 24) and female (n = 10) patients from the POSEIDON-DCM trial who received MSCs via transendocardial injections were evaluated over 12 months. Endothelial function was measured at baseline and 3 months post-transendocardial stem cell injection (TESI). At baseline, ejection fraction (EF) was lower (P = 0.004) and end-diastolic volume (EDV; P = 0.0002) and end-systolic volume (ESV; P = 0.0002) were higher in males vs. females. In contrast, baseline demographic characteristics, Minnesota Living with Heart Failure Questionnaire (MLHFQ), and 6-min walk test (6MWT) were similar between groups. EF improved in males by 6.2 units (P = 0.04) and in females by 8.6 units (P = 0.04; males vs. females, P = 0.57). EDV and ESV were unchanged over time. The MLHFQ score, New York Heart Association (NYHA)

class, endothelial progenitor cell-colony forming units, and serum tumour necrosis factor alpha improved similarly in both groups. CONCLUSION: Despite major differences in phenotypic presentation of NIDCM in males and females, this study is the first of its kind to demonstrate that MSC therapy improves a variety of parameters in NIDCM irrespective of patient sex. These findings have important clinical and pathophysiologic implications regarding the impact of sex on responses to cell-based therapy for NIDCM.

Garces Ambrossi, G., et al. (2005). "Active tuberculosis limited to foreign-born patients after allogeneic hematopoietic stem cell transplant." Bone Marrow Transplant **36**(8): 741-743.

Goldberg, J. D., et al. (2013). "Palifermin is efficacious in recipients of TBI-based but not chemotherapy-based allogeneic hematopoietic stem cell transplants." Bone Marrow Transplant **48**(1): 99-104.

Palifermin, a recombinant human keratinocyte growth factor, is commonly given to prevent mucositis following autologous transplantation. In the allogeneic hematopoietic stem cell transplant (allo-HSCT) setting, safety and efficacy data are limited. We conducted a retrospective study in 251 patients undergoing allo-HSCT, 154 of whom received peritransplant palifermin. In all patients, palifermin significantly decreased the mean number of days of total parenteral nutrition (TPN, 13 vs 16 days, P=0.006) and patient-controlled analgesia (PCA, 6 vs 10 days, P=0.023), as well as the length of initial hospital stay (LOS, 32 vs 37 days, P=0.014). However, the effect of palifermin was only significant in patients who received a TBI- but not BU-based chemotherapy conditioning regimen. In TBI recipients, palifermin decreased the mean number of days of TPN (13 vs 17 days, P<0.001) and PCA (7 vs 12 days, P=0.033), and the length of stay (32 vs 38 days, P=0.001). Palifermin did not affect GVHD, graft failure or relapse. Therefore, in the largest analysis with this patient population to date, we demonstrate that palifermin is safe in allo-HSCT patients, decreases TPN and PCA use and decreases LOS following TBI-based but not chemotherapy-based allo-HSCT.

Haddad, F., et al. (2015). "Immunologic Network and Response to Intramyocardial CD34+ Stem Cell Therapy in Patients With Dilated Cardiomyopathy." J Card Fail **21**(7): 572-582.

BACKGROUND: Although stem cell therapy (SCT) is emerging as a potential treatment for patients with dilated cardiomyopathy (DCM), clinical response remains variable. Our objective was to determine whether baseline differences in circulating immunologic and nonimmunologic biomarkers may help to identify patients more likely to respond to intramyocardial injection of CD34(+)-based SCT. METHODS AND RESULTS: We enrolled from January 3, 2011 to March 5, 2012 37 patients with longstanding DCM (left ventricular ejection fraction [LVEF] <40%, New York Heart Association functional class III) who underwent peripheral CD34(+) stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) and collection by means of apheresis. CD34(+) cells were labeled with (99m)Tc-hexamethylpropyleneamine oxime to allow assessment of stem cell retention at 18 hours. Response to SCT was predefined as an increase in LVEF of >/=5% at 3 months. The majority (84%) of patients were male with an overall mean LVEF of 27 +/- 7% and a median N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 2,774 pg/mL. Nineteen patients (51%) were responders to SCT. There was no significant difference between responders and nonresponders regarding to age, sex, baseline LVEF, NT-proBNP levels, or 6-minute walking distance. With the use of a partial least squares (PLS) predictive model, we identified 9 baseline factors that were associated with both stem cell response and stem cell retention (mechanistic validation). Among the baseline factors positively associated with both clinical response and stem cell retention were G-CSF, SDF-1, LIF, MCP-1, and MCP-3. Among baseline factors negatively associated with both clinical response and retention were IL-12p70, FASL, ICAM-1, and GGT. A decrease in G-CSF at 3-month follow-up was also observed in responders compared with nonresponders (P = .02). CONCLUSIONS: If further validated, baseline immunologic and nonimmunologic biomarkers may help to identify patients with DCM who are more likely to respond to CD34(+)-based SCT.

Hall, Z. W., et al. (2010). "Breaking ground on translational stem cell research." Ann N Y Acad Sci **1189 Suppl 1**: E1-15.

Sponsored by the New York Stem Cell Foundation (NYSCF), the "Fourth Annual Translational Stem Cell Research Conference: Breaking Ground" convened October 13-14, 2009 at The Rockefeller University in New York City to discuss translational stem cell research. Attracting over 400 scientists, patient advocates, and stem cell research supporters from fifteen countries, the two-day conference featured an afternoon of panel discussions, intended for a broad audience, followed by a second day of scientific talks and poster presentations. This report summarizes both days of this exciting conference.

Hong, K. U. and R. Bolli (2014). "Cardiac stem cell therapy for cardiac repair." Curr Treat Options Cardiovasc Med **16**(7): 324.

OPINION STATEMENT: The discovery of adult cardiac stem cells (CSCs) and their potential to restore functional cardiac tissue has fueled unprecedented interest in recent years. Indeed, stem-cell-based therapies have the potential to transform the treatment and prognosis of heart failure, for they have the potential to eliminate the underlying cause of the disease by reconstituting the damaged heart with functional cardiac cells. Over the last decade, several independent laboratories have demonstrated the utility of c-kit+/Lin- resident CSCs in alleviating left ventricular dysfunction and remodeling in animal models of acute and chronic myocardial infarction. Recently, the first clinical trial of autologous CSCs for treatment of heart failure resulting from ischemic heart disease (Stem Cell Infusion in Patients with Ischemic cardiOmyopathy [SCIPIO]) has been conducted, and the interim results are quite promising. In this phase I trial, no adverse effects attributable to the CSC treatment have been noted, and CSC-treated patients showed a significant improvement in ejection fraction at 1 year (+13.7 absolute units versus baseline), accompanied by a 30.2 % reduction in infarct size. Moreover, the CSC-induced enhancement in cardiac structure and function was associated with a significant improvement in the New York Heart Association (NYHA) functional class and in the quality of life, as measured by the Minnesota Living with Heart failure Questionnaire. These results are exciting and warrant larger, phase II studies. However, CSC therapy for cardiac repair is still in its infancy, and many hurdles need to be overcome to further enhance the therapeutic efficacy of CSCs.

Hoppe, B. S., et al. (2008). "Involved-field radiotherapy before high-dose therapy and autologous stem-cell rescue in diffuse large-cell lymphoma: long-term disease control and toxicity." J Clin Oncol **26**(11): 1858-1864.

PURPOSE: To analyze outcome, prognostic factors, and toxicities in patients with diffuse large-cell lymphoma (DLCL) who received involved-field radiotherapy (IFRT) before high-dose chemotherapy with autologous stem-cell rescue (ASCR). PATIENTS AND METHODS: Between January 1990 and August 2006, 164 patients with relapsed or refractory DLCL received IFRT at Memorial Sloan-Kettering Cancer Center (New York, NY) before high-dose chemotherapy and ASCR. IFRT was delivered to involved sites measuring more than 5 cm or to sites with residual disease more than 2 cm. Radiotherapy was administered in 1.5-Gy fractions twice daily to a total dose of 30 Gy. Progression-free survival and overall survival were calculated, and short- and long-term toxicity was assessed according to National Cancer Institute Common Toxicity Criteria (version 2.0). Median follow-up was 60 months (range, 2 to 187 months). RESULTS: Two- and 5-year progression-free survival was 62% and 53%; 2- and 5-year overall survival was 67% and 58%, respectively. Sixty-seven patients relapsed; only 10 patients relapsed completely within the radiotherapy field. There were seven early treatment-related mortalities and 11 secondary cancers (including four myelodysplastic syndromes), one of which occurred within the IFRT site and five after total-body irradiation. CONCLUSION: Minimal treatment-related mortality and morbidity resulted from short, intensive, involved-field radiotherapy before high-dose chemotherapy and ASCR, which was incorporated into a salvage regimen for patients with relapsed/refractory DLCL. This chemoradiotherapy salvage regimen resulted in a low local relapse rate that could potentially translate into an improved total outcome.

Huttmann, A., et al. (2006). "Granulocyte colony-stimulating factor-induced blood stem cell mobilisation in patients with chronic heart failure--Feasibility, safety and effects on exercise tolerance and cardiac function." Basic Res Cardiol **101**(1): 78-86.

Bone marrow-derived stem cells may contribute to the regeneration of non-haematopoietic organs. In order to test whether an increase in circulating stem cell numbers improves impaired myocardial function we treated 16 male patients with chronic heart failure due to dilated (DCM; n = 7) or ischaemic cardiomyopathy (ICM; n = 9) with the stem cell mobilising cytokine granulocyte colony-stimulating factor (G-CSF; four 10-day treatment periods interrupted by treatment-free intervals of equal length). Safety and efficacy analyses were performed at regular intervals. Peak CD34+ cell counts remained constant from cycle to cycle. Cardiac side effects in ICM patients included occasional episodes of dyspnea or angina and one episode of fatal ventricular fibrillation. Nine (4 DCM, 5 ICM) of 12 patients receiving four full G-CSF cycles experienced an improvement by one New York Heart Association (NYHA) class and a statistically significant increase in six-minute walking distance. By contrast, none of 8 ICM historical controls had a change in NYHA class during a similar time period. Statistically significant changes in echocardiographic parameters were not recorded. Sequential administration of G-CSF is feasible and possibly effective in improving physical performance in patients with chronic heart failure. Patients with ICM may be at risk of increased angina and arrhythmias.

Jathavedam, A., et al. (2008). "Infectious complications from high-dose chemotherapy and autologous stem cell

transplantation for metastatic germ cell tumors." Biol Blood Marrow Transplant **14**(5): 595-600.

High-dose chemotherapy with autologous stem cell transplantation (ASCT) is increasingly utilized in patients with relapsed and refractory germ cell tumors (GCT). Infectious complications are common after ASCT for hematologic malignancies, but their epidemiology in GCT patients has not been described. To identify infectious complications of ASCT for GCT, we conducted a retrospective study of patients treated at our institution, a tertiary-care cancer center in New York City between 1994 and 2006. Patients received ciprofloxacin prophylaxis but no routine antifungal or antiviral prophylaxis. In addition, patients were housed in shared rooms of 2 with standard precautions during hospitalizations. Overall, 107 patients with relapsed or refractory GCT were treated with 1-2 cycles of paclitaxel/ifosfamide and 1-3 cycles of high-dose carboplatin/etoposide with ASCT. Sixty (56%) of 107 patients developed 95 total infections, including 33 catheter-associated bloodstream infections. Fungal, viral, and nosocomial infections were uncommon. There were no infection-related deaths. In conclusion, serious morbidity from infection is uncommon among GCT patients receiving high-dose chemotherapy with ASCT. Isolation and aggressive antifungal and antiviral prophylaxis is not warranted in these patients.

Khaddour, K., et al. (2022). Hematopoietic Stem Cell Transplantation. StatPearls. Treasure Island (FL).

Bone marrow transplant (hematopoietic stem cell transplant) (HPSCT) involves the administration of healthy hematopoietic stem cells in patients with dysfunctional or depleted bone marrow. This helps to augment bone marrow function and allows, depending on the disease being treated, to either destroy tumor cells with malignancy or to generate functional cells that can replace the dysfunctional ones in cases like immune deficiency syndromes, hemoglobinopathies, and other diseases. History and Evolution Hematopoietic stem cell transplantation (HSCT) was first explored in humans in the 1950s and was based on observational studies in mice models which showed that infusion of healthy bone marrow components into a myelosuppressed bone marrow could induce recovery of its function in the recipient.[1] These animal-based studies soon found their clinical application into humans when the first successful bone marrow transplant was performed in monozygotic twins in New York in 1957 (syngeneic transplant) in a patient with acute leukemia.[2] As a result, the physician Dr. Thomas who performed the procedure continued his research on the development of bone marrow transplantation and later received the Nobel Prize of physiology and medicine in appreciation of his work. The first successful allogeneic bone marrow transplant was reported in Minnesota in 1968 for a pediatric patient with severe, combined immunodeficiency syndrome.[3] Since then, allogeneic and autologous stem cell transplant has increased in the United States and worldwide. The Center for International Blood and Marrow Transplant Research (CIBMTR) reported over 8000 allogenic transplants performed in the United States in 2016 with a higher number of autologous transplants with a steady and higher increase of autologous compared to allogenic.[4] Definitions Major Histocompatibility Complex (MHC) The group of genes on the short arm of chromosome 6 (p6) that encodes human leukocyte antigens (HLA) which are considered being highly polymorphic leading to a large difference in the resultant expressed proteins on human cells. They are divided into MHC I and MHC II Human Leukocyte Antigens (HLA) These are the proteins expressed on the cellular surface and play an important role in alloimmunity. HLA can be divided into (HLA-A, B, and C) which are encoded by class I MHC and are expressed on all cell types and present peptides derived from the cytoplasm and are recognized by CD8+ T cells. The other HLA type is classified as (HLA- DP, DQ, and DR) which are encoded by MHC II and can be found on antigen-presenting cells (APCs) and this class is recognized by CD4+ T cells. Syngeneic Bone Marrow Transplantation The donor and the recipient are identical twins. The advantages include no graft versus host disease (GVHD) and no graft failure. However, only a tiny number of transplant patients will have the ability to have an identical twin for transplantation. Autologous Bone Marrow Transplantation The bone marrow products are collected from the patient and are reinfused after purification methods. The advantages include no GVHD. The disadvantage is that the bone marrow products may contain abnormal cells that can cause relapse in the case of malignancy hence; theoretically, this method cannot be used in all cases of abnormal bone marrow diseases. Allogenic Transplantation The donor is an HLA matched family member, unrelated matched donor or mismatched family donors (haploidentical). Engraftment The process of which infused transplanted hematopoietic stem cells produce mature progeny in the peripheral circulation Preparative Regimen This is a regimen that comprises high-dose chemotherapy and/or total body irradiation (TBI) which are administered to the recipient prior to stem cell infusion to eliminate the largest number of malignant cells and to allow for immunosuppression in the recipient so that engraftment can occur.

Klitzman, R. and M. V. Sauer (2009). "Payment of egg donors in stem cell research in the USA." Reprod Biomed Online **18**(5): 603-608.

Arguments have been put forth as to whether women who donate oocytes for human embryonic stem cell (HESC) research should be compensated, but data regarding this issue have been scant. Recently in the United States, several States have begun funding HESC research, and patient recruitment efforts have begun. This paper lays out relevant arguments and presents data concerning this issue. Researchers are finding that women are unwilling to donate eggs altruistically, which is hampering the progress of research. These efforts are examined, and data on potential donors' views are presented. The absence of payment, rather than ethical concerns, appears to explain opposition to donation. Women also appear generally ignorant of policies in this area. It is suggested that policy discussions shift focus from whether to pay, to how much would be appropriate, and how to decide; and that research and public and professional education be increased to heighten understanding and awareness of these issues.

Knowlton, D. (2010). "Fifth Annual Stem Cell Summit." IDrugs **13**(4): 235-238.

The Fifth Annual Stem Cell Summit, held in New York, included topics covering new commercial developments in the research field of stem cell-based therapies. This conference report highlights selected presentations on embryonic and adult stem cells, stem cell-based therapies for the treatment of orthopedic and cardiovascular indications and inflammatory diseases, as well as technologies for processing and storing stem cells. Investigational therapies discussed include placental expanded (PLX) cells (Pluristem Therapeutics Inc), StemEx (Gamida-Teva Joint Venture/Teva Pharmaceutical Industries Ltd) and remestemcel-L (Osiris Therapeutics Inc/Genzyme Corp/JCR Pharmaceuticals Co Ltd/ Mochida Pharmaceutical Co Ltd).

Kurtzberg, J., et al. (1994). "The use of umbilical cord blood in mismatched related and unrelated hemopoietic stem cell transplantation." Blood Cells **20**(2-3): 275-283; discussion 284.

Over the past 6 years, umbilical cord blood has emerged as an efficacious alternative source of hematopoietic stem cells in related bone marrow transplantation. These encouraging results led us to extend this technology to the mismatched related and unrelated settings in three high-risk leukemic children lacking a matched-related donor for transplantation. Two of the three children also lacked identifiable donors through the National Marrow Donor Program, while the third was in relapse and did not have time to wait for completion of a search. The first child was transplanted with haploidentical umbilical cord blood-derived mononuclear cells from his sister, while the remaining two children were transplanted with partially mismatched, unseparated, unrelated umbilical cord blood banked through the Placental Blood Project at the New York Blood Center. All three children demonstrated trilineage engraftment with donor cells within 6 weeks of transplantation. The patient transplanted with haploidentical marrow developed grade 2 graft vs. host disease (GVHD), which was controlled with steroid and anti-thymocyte globulin (ATG) therapy. One of the two patients grafted with unrelated umbilical cord blood developed mild grade 1 GVHD of the skin, which rapidly cleared with steroid therapy. One patient remains alive, in good health and disease-free 12 months from transplantation.

Lahoud, O. B., et al. (2021). "Reduced-intensity conditioning hematopoietic stem cell transplantation for chronic lymphocytic leukemia and Richter's transformation." Blood Adv **5**(14): 2879-2889.

Allogeneic hematopoietic stem cell transplantation (HSCT) may potentially cure patients with chronic lymphocytic leukemia (CLL) and Richter's transformation (CLL-RT) or CLL without RT, but the impact of novel agents on HSCT is unclear. CLL-RT patients have a grave prognosis, and their outcomes after HSCT are uncertain. We conducted a retrospective analysis of all 58 CLL patients, including 23 CLL-RT patients, who underwent reduced intensity conditioning (RIC) HSCT at Memorial Sloan Kettering Cancer Center (New York, NY) between September 2006 and April 2017. With a median follow-up of 68 months (range, 24-147 months), 5-year progression-free survival (PFS) was 40% (95% confidence interval [CI], 28%-56%), and overall survival (OS) was 58% (95% CI, 48%-74%). The 1-year graft-versus-host disease/relapse-free survival (GRFS) was 38% (95% CI, 25%-50%). Patients with CLL-RT and CLL patients without RT had comparable outcomes. In both cohorts, treatment-sensitive response and </=3 previous lines of therapy produced superior PFS and OS. Outcomes were agnostic to adverse cytogenetic and molecular features. Novel agents did not have a negative impact on HSCT outcomes. Total body irradiation (TBI)-containing RIC yielded inferior PFS, OS, and GRFS. CLL-RT patients older than age 55 years who had an HSCT Comorbidity Index score of >/=2 demonstrated inferior OS. This study, which is the largest series of RIC-HSCT for patients with CLL-RT, provides evidence supporting RIC-HSCT in early remission courses for patients with CLL-RT and poor-risk CLL patients. TBI-containing RIC should be considered with caution.

Liao, C., et al. (2006). "[Results of unrelated umbilical cord blood stem cell transplantation for 65 patients in China]." Zhonghua Er Ke Za Zhi **44**(3): 220-223.

OBJECTIVE: From December 1998 to April 2004, 3960 umbilical cord blood units were stored in Guangzhou cord blood bank, which provided 100 umbilical cord blood units to 25 transplant center for 83 patients with malignant or non-malignant diseases. To study the related factors affecting unrelated umbilical cord blood stem cell transplantation, the authors analyzed retrospectively the results of transplantation of unrelated umbilical cord blood stem cells for 65 patients. METHODS: ALL (acute lymphocytic leukemia) cord blood units were obtained from full term normal vaginal and cesarean deliveries in Guangzhou Women and Infants Hospital. The fractionation, cryopreservation and thawing of the cord blood were performed according to the regulations of New York umbilical cord blood bank and pertinent literature. The selection of cord blood was based on HLA typing and the number of nucleated cells. The sex and HLA antigens of donors were defined as the evidence of engraftment. Time to engraftment was recorded when the absolute number of neutrophil ANC (absolute neutrophil count) was higher than 5.0 x 10(8) for three days. Event-free survival and graft versus host disease (GVHD) were provided by transplant centers. RESULTS: Out of 65 patients who received unrelated cord blood stem cell transplant, 49 patients were diagnosed as having malignant diseases [including 23 with ALL, 16 with AML (acute myeloid leukemia), 7 with CML (chronic myelogenous leukemia), 3 with lymphoma and one with MDS (myelodysplastic syndrome)], 16 patients had non-malignant disease. The 65 transplanted patients (42 male, 23 female) had a median age of 10 years (range 1 - 33 years) and a median body weight of 27 kg (range 10 - 67 kg). The patients received cord blood stem cells from unrelated 0-locus (n = 9) or 1-locus (n = 43) or 2-locus (n = 13) HLA mismatched donor. The median dose of infused cells was: total neutrophil count (TNC) 5.7 x 10(7), CD(34)(+) 5.1 x 10(5), CFU-GM 3.8 x 10(4). Fifty of 65 (77%) patients had engraftment. GVHD occurred in 41 patients (63%), including acute grade I - II GVHD in 31 patients (76%), acute grade III - IV GVHD in 8 patients (20%) and chronic GVHD in 2 patients (5%). Fifty patients had engraftment (ANC > 5.0 x 10(8)) after a median time of 17 (range 7 to 44) days after transplant, while an autologous hematopoietic reconstitution was observed in 6 patients; 24 patients died of severe pneumonia (n = 8), acute GVHD (n = 4), or sepsis (n = 12) and the disease-free survival probability was 61%. CONCLUSIONS: Unrelated allogeneic umbilical cord blood transplantation may be a good substitution for unrelated allogeneic bone marrow transplantation with a good prospect.

Lisenko, K., et al. (2017). "Comparison of Different Stem Cell Mobilization Regimens in AL Amyloidosis Patients." Biol Blood Marrow Transplant **23**(11): 1870-1878.

High-dose melphalan (HDM) and autologous blood stem cell transplantation (ABSCT) is an effective treatment for transplantation-eligible patients with systemic light chain (AL) amyloidosis. Whereas most centers use granulocyte colony-stimulating factor (G-CSF) alone for mobilization of peripheral blood stem cells (PBSC), the application of mobilization chemotherapy might offer specific advantages. We retrospectively analyzed 110 patients with AL amyloidosis who underwent PBSC collection. Major eligibility criteria included age <70 years and cardiac insufficiency New York Heart Association </=III degrees . Before mobilization, 67 patients (61%) had been pretreated with induction therapy, including 17 (15%) patients who had received melphalan. Chemo-mobilization was performed with either cyclophosphamide, doxorubicin, dexamethasone (CAD)/G-CSF (n = 78, 71%); ifosfamide/G-CSF (n = 14, 13%); or other regimens (n = 8, 7%). AL amyloidosis patients with predominant heart involvement and/or status post heart transplantation were mobilized with G-CSF only (n = 10, 9%). PBSC collection was successful in 101 patients (92%) at first attempt. The median number of CD34(+) cells was 8.7 (range, 2.1 to 45.5) x 10(6) CD34(+)/kg collected in a median of 1 leukapheresis (LP) session. Compared with G-CSF-only mobilization, a chemo-mobilization with CAD/G-CSF or ifosfamide/G-CSF had a positive impact on the number of collected CD34(+) cell number/kg per LP (P <.001, multivariate). Melphalan-containing previous therapy and higher age had a significant negative impact on quantity of collected CD34(+) cells. Median common toxicity criteria (CTC) grade of nonhematologic toxicity was II (range, 0 to IV). Life-threatening CTC grade IV adverse events were observed in 3 patients with no fatalities. Cardiovascular events were observed in 17 patients (22%) upon CAD/G-CSF mobilization (median CTC: grade 3; range, 1 to 4). Toxicity in patients undergoing ifosfamide/G-CSF mobilization was higher than in with those who received G-CSF-only mobilization. HDM and ABSCT were performed in 100 patients. Compared with >6.5 x 10(6) transplanted CD34(+) cells/kg, an ABSCT with <3 x 10(6) CD34(+) cells/kg was associated with a longer duration to leukocyte reconstitution >1 x 10(9)/L and a reduced platelet count <150 x 10(9)/L 1 year after ASCT. Our results show that CAD chemotherapy is very effective in PBSC mobilization and has a tolerable toxicity profile in AL amyloidosis patients. A further toxicity reduction by omission of doxorubicin might be considered. Because

of advanced nonhematologic toxicity, ifosfamide administration cannot be recommended. However, G-CSF mobilization alone is also safe and effective. Considering the hematopoietic reconstitution and long-term stem cell function, our results provide a rationale to collect and transplant as many as >6.5 x 10(6) CD34(+) cells/kg, if feasible with reasonable effort.

Lopez, M. C. and D. A. Lawrence (2008). "Proficiency testing experience for viable CD34+ stem cell analysis." Transfusion **48**(6): 1115-1121.

BACKGROUND: Successful hematopoietic engraftment depends on the number of viable CD34+ stem cells. Therefore, accurate quantification of viable CD34+ stem cells is required. STUDY DESIGN AND METHODS: To evaluate clinical laboratory performance, the New York State Department of Health initiated proficiency testing (PT) for viable CD34+ stem cells. Preserved adult peripheral blood was spiked with preserved cord blood CD34+ stem cells and was shipped to the participating laboratories. Three educational and two graded PTs were performed by participating laboratories, and their results were analyzed for consistency. Comparative analysis of viability with 7-aminoactinomycin D (7-AAD) and ToPro-3 dyes also was performed. RESULTS: Laboratories had to adapt their standard operating procedures to include a viability dye to quantify the number of viable CD34+ stem cells. The majority of laboratories chose 7-AAD as their preferred viability dye, but propidium iodide (PI) and ToPro-3 were used by two laboratories. Once all laboratories started to simultaneously analyze viability and staining for CD34, graded PTs started. Lower numbers of viable CD34+ stem cells were obtained for ToPro-3 when the dye was compared with 7-AAD. CONCLUSION: It is concluded that ToPro-3 stains more cells than 7-AAD and likely includes compromised cells. The use of new vital dyes, like ToPro-3, that may stain preapoptotic cells could represent an important advance to improve the quantification of viable CD34+ stem cells, for engraftment purposes. Further studies are needed to document the benefits of switching to a method that excludes not only dead cells, but apoptotic cells as well.

Massey, R. J., et al. (2020). "Left Ventricular Systolic Function in Long-Term Survivors of Allogeneic Hematopoietic Stem Cell Transplantation." JACC CardioOncol **2**(3): 460-471.

BACKGROUND: Allogeneic hematopoietic stem cell transplantation (allo-HSCT), a potentially curative therapy for malignant and nonmalignant diseases, is being increasingly used in younger patients. Although allo-HSCT survivors have an established increased risk of cardiovascular disease, there is limited knowledge of the long-term effects on cardiac function in survivors. OBJECTIVES: The purpose of this study was to describe left ventricular (LV) systolic function in long-term allo-HSCT survivors treated in childhood, adolescence, or early adulthood. METHODS: Our cross-sectional cohort study included 104 patients (56% women), age 18 +/- 10 years at time allo-HSCT with 17 +/- 6 years of follow-up. Echocardiography included 2-dimensional (2D) and 3-dimensional (3D) analyses and speckle tracking imaging. In total, 55 healthy control subjects with a similar age, sex, and body mass index were used for comparison. Left ventricular systolic dysfunction (LVSD) was defined as reduced 2D left ventricular ejection fraction (LVEF) of <52% in men and <54% in women, and/or a reduced global longitudinal strain (GLS) of >/=-17%. Multivariable linear regression was used to determine independent predictors of 2D-LVEF and GLS. RESULTS: Allo-HSCT survivors had significantly reduced LV systolic function compared with control subjects: 2D-LVEF (55.2 +/- 5.8% vs. 59.0 +/- 2.9%; $p < 0.001$), 3D LVEF (54.0 +/- 5.1% vs. 57.6 +/- 2.7%; $p < 0.001$), and GLS (-17.5 +/- 2.2% vs. -19.8 +/- 1.4%; $p < 0.001$). LVSD was found in 44.2%, of whom 28.3% were symptomatic. Clinical factors independently associated with 2D-LVEF and/or GLS included age, anthracyclines, graft versus host disease (GVHD), heart rate, and hypertension. In the 45% of survivors pre-treated with anthracyclines, the effect of anthracyclines on 2D-LVEF and GLS was dose-dependent. CONCLUSIONS: LVSD is common in long-term survivors of allo-HSCT treated in their youth. Pre-HSCT therapies with anthracyclines, age, heart rate, hypertension, and graft versus host disease are associated with measures of LV function.

Menasche, P., et al. (2015). "Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report." Eur Heart J **36**(30): 2011-2017.

AIMS: Comparative studies suggest that stem cells committed to a cardiac lineage are more effective for improving heart function than those featuring an extra-cardiac phenotype. We have therefore developed a population of human embryonic stem cell (ESC)-derived cardiac progenitor cells. METHODS AND RESULTS: Undifferentiated human ESCs (I6 line) were amplified and cardiac-committed by exposure to bone morphogenetic protein-2 and a fibroblast growth factor receptor inhibitor. Cells responding to these cardio-instructive cues express the cardiac transcription factor Isl-1 and the stage-specific embryonic antigen SSEA-1 which was then used to purify them by immunomagnetic sorting. The Isl-1(+) SSEA-1(+) cells were then embedded into a fibrin scaffold which was surgically delivered onto the infarct area in a 68-year-old patient suffering from severe heart failure [New

York Heart Association [NYHA] functional Class III; left ventricular ejection fraction (LVEF): 26%]. A coronary artery bypass was performed concomitantly in a non-infarcted area. The implanted cells featured a high degree of purity (99% were SSEA-1(+)), had lost the expression of Sox-2 and Nanog, taken as markers for pluripotency, and strongly expressed Isl-1. The intraoperative delivery of the patch was expeditious. The post-operative course was uncomplicated either. After 3 months, the patient is symptomatically improved (NYHA functional Class I; LVEF: 36%) and a new-onset contractility is echocardiographically evident in the previously akinetic cell/patch-treated, non-revascularized area. There have been no complications such as arrhythmias, tumour formation, or immunosuppression-related adverse events. CONCLUSION: This observation demonstrates the feasibility of generating a clinical-grade population of human ESC-derived cardiac progenitors and combining it within a tissue-engineered construct. While any conclusion pertaining to efficacy would be meaningless, the patient's functional outcome yet provides an encouraging hint. Beyond this case, the platform that has been set could be useful for generating different ESC-derived lineage-specific progenies.

Miyagawa, S., et al. (2017). "Phase I Clinical Trial of Autologous Stem Cell-Sheet Transplantation Therapy for Treating Cardiomyopathy." J Am Heart Assoc **6**(4).

BACKGROUND: When transplanted into failing heart, autologous somatic tissue-derived cells yield functional recovery via paracrine effects that enhance native regeneration. However, the therapeutic effects are modest. We developed a method in which scaffold-free cell sheets are attached to the epicardial surface to maximize paracrine effects. This Phase I clinical trial tested whether transplanting autologous cell-sheets derived from skeletal muscle is feasible, safe, and effective for treating severe congestive heart failure. METHODS AND RESULTS: Fifteen ischemic cardiomyopathy patients and 12 patients with dilated cardiomyopathy, who were in New York Heart Association functional class II or III and had been treated with the maximum medical and/or interventional therapies available, were enrolled. Scaffold-free cell sheets of 3 to 9x10(8) cells derived from autologous muscle were transplanted over the LV free wall via left thoracotomy, without additional interventional treatments. There were no procedure-related major complications during follow-up. The majority of the ischemic cardiomyopathy patients showed marked symptomatic improvement in New York Heart Association classification (pre: 2.9+/-0.5 versus 6 months: 2.1+/-0.4, P<0.01; 1 year: 1.9+/-0.3, P<0.01) and the Six-Minute Walk Test with significant reduction of serum brain natriuretic peptide level (pre: 308+/-72 pg/mL versus 6 months: 191+/-56 versus 1 year: 182+/-46, P<0.05), pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vein resistance, and left ventricular wall stress after transplantation instead of limited efficacy in dilated cardiomyopathy patients. CONCLUSIONS: Cell-sheet transplantation as a sole therapy was feasible for treating cardiomyopathy. Promising results in the safety and functional recovery warrant further clinical follow-up and larger studies to confirm this treatment's efficacy for severe congestive heart failure. CLINICAL TRIAL REGISTRATION: URL: http://www.umin.ac.jp/english/. Unique identifier: UMIN000003273.

Modak, S., et al. (2004). "Thiotepa-based high-dose chemotherapy with autologous stem-cell rescue in patients with recurrent or progressive CNS germ cell tumors." J Clin Oncol **22**(10): 1934-1943.

PURPOSE: To evaluate the efficacy and toxicity of high-dose chemotherapy (HDC) followed by autologous stem-cell rescue (ASCR) in patients with relapsed or progressive CNS germ cell tumors (GCTs). PATIENTS AND METHODS: Twenty-one patients with CNS GCTs who experienced relapse or progression despite having received initial chemotherapy and/or radiotherapy were treated with thiotepa-based HDC regimens followed by ASCR. RESULTS: Estimated overall survival (OS) and event-free survival (EFS) rates for the entire group 4 years after HDC were 57% +/- 12% and 52% +/- 14%, respectively. Seven of nine (78%) patients with germinoma survived disease-free after HDC with a median survival of 48 months. One patient died as a result of progressive disease (PD) 39 months after HDC, and another died as a result of pulmonary fibrosis unrelated to HDC 78 months after ASCR without assessable disease. However, only four of 12 patients (33%) with nongerminomatous germ cell tumors (NGGCTs) survived without evidence of disease, with a median survival of 35 months. Eight patients with NGGCTs died as a result of PD, with a median survival of 4 months after HDC (range, 2 to 17 months). Patients with germinoma fared better than those with NGGCTs (P =.016 and.014 for OS and EFS, respectively). Patients with complete response to HDC also had significantly better outcome (P <.001 for OS and EFS) compared with patients with only a partial response or stable disease. There were no toxic deaths because of HDC. CONCLUSION: Dose escalation of chemotherapy followed by ASCR is effective therapy for patients with recurrent CNS germinomas and might be effective in patients with recurrent NGGCTs with a low tumor burden.

Mohyeddin-Bonab, M., et al. (2007). "Autologous in vitro expanded mesenchymal stem cell therapy for human old myocardial infarction." Arch Iran Med **10**(4): 467-473.

BACKGROUND: Stem cell transplantation after myocardial infarction has been claimed to restore cardiac function. Mesenchymal stem cells attract a lot of attention because of the feasibility of in vivo and ex vivo differentiation to cardiomyocytes and endothelial cells as well as their trophic effect on tissue repair. In this study, we investigated the efficacy of autologous bone marrow derived mesenchymal stem cells in improving heart function in patients with old myocardial infarction. METHODS: Eight patients with old myocardial infarction and proper inclusion criteria were injected with mesenchymal stem cells at the time of coronary artery bypass grafting or percutaneous coronary intervention (test group) and compared with eight matched patients who received the same treatment without mesenchymal stem cell injection (control group). Evaluation of heart function was done by echocardiography plus single-photon emission computed tomography before and six months after the procedure. Serial clinical examination was performed every month through New York Heart Association class. RESULTS: The mean New York Heart Association class and single-photon emission computed tomography scan results decreased significantly in the test group (P=0.000 and 0.002, respectively) and in the control group (P=0.049 and 0.007, respectively) after the procedure at six months follow-up. Left ventricular ejection fraction increased significantly in the test group (P= 0.005) but not in the control group. In comparison between the test and control groups the results of New York Heart Association class assessment and single-photon emission computed tomography demonstrated significant improvement in the test group (P=0.005 and 0.013, respectively). There were no significant differences between the baseline variables in the two groups. CONCLUSION: Transplantation of ex vivo expanded bone marrow derived mesenchymal stem cell in patients with old myocardial infarction is a safe and feasible procedure. These cells improve the cardiac function without serious adverse effects.

Murbraech, K., et al. (2015). "Heart Failure and Asymptomatic Left Ventricular Systolic Dysfunction in Lymphoma Survivors Treated With Autologous Stem-Cell Transplantation: A National Cross-Sectional Study." J Clin Oncol **33**(24): 2683-2691.

PURPOSE: We aimed to determine the prevalence of left ventricular systolic dysfunction (LVSD), including symptomatic (ie, heart failure [HF]) and asymptomatic LVSD in adult lymphoma survivors (LSs) after autologous hematopoietic stem-cell transplantation (auto-HCT) and to identify risk factors for LVSD in this population. PATIENTS AND METHODS: All LSs treated with auto-HCT as adults in Norway from 1987 to 2008 were eligible for this national cross-sectional study. Asymptomatic LVSD was defined as left ventricular ejection fraction less than 50% by echocardiography, and HF was defined according to current recommendations. The results in LSs were compared with those found in an age- and sex-matched (1:1) control group. RESULTS: We examined 274 LSs (69% of all eligible survivors); 62% were men, the mean (+/- standard deviation) age was 56 +/- 12 years, and mean follow-up time from lymphoma diagnosis was 13 +/- 6 years. The mean cumulative doxorubicin dose was 316 +/- 111 mg/m(2), and 35% of LSs had received additional radiation therapy involving the heart. We found LVSD in 15.7% of the LSs, of whom 5.1% were asymptomatic. HF patients were symptomatically mildly affected, with 8.8% of all LSs classified as New York Heart Association class II, whereas more severe HF was rare (1.8%). Compared with controls, LSs had a substantially increased LVSD risk (odds ratio, 6.6; 95% CI, 2.5 to 17.6; P < .001). A doxorubicin dose >/= 300 mg/m(2) and cardiac radiation therapy dose greater than 30 Gy were independent risk factors for LVSD. CONCLUSION: LVSD was frequent and HF more prevalent than previously reported in LSs after auto-HCT. Our results may help to identify LSs at increased LVSD risk and can serve as a basis for targeted surveillance strategies.

Nyolczas, N., et al. (2007). "Design and rationale for the Myocardial Stem Cell Administration After Acute Myocardial Infarction (MYSTAR) Study: a multicenter, prospective, randomized, single-blind trial comparing early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of nonselected autologous bone marrow cells to patients after acute myocardial infarction." Am Heart J **153**(2): 212 e211-217.

BACKGROUND: Previous data suggest that bone marrow-derived stem cells (BM-SCs) decrease the infarct size and beneficially affect the postinfarction remodeling. METHODS: The Myocardial Stem Cell Administration After Acute Myocardial Infarction Study is a multicenter, prospective, randomized, single-blind clinical trial designed to compare the early and late intracoronary or combined (percutaneous intramyocardial and intracoronary) administration of BM-SCs to patients after acute myocardial infarction (AMI) with reopened infarct-related artery. The primary end points are the changes in resting myocardial perfusion defect size and left ventricular ejection fraction (gated single photon emission computed tomography [SPECT] scintigraphy)

3 months after BM-SCs therapy. The secondary end points relate to evaluation of (1) the safety and feasibility of the application modes, (2) the changes in left ventricular wall motion score index (transthoracic echocardiography), (3) myocardial voltage and segmental wall motion (NOGA mapping), (4) left ventricular end-diastolic and end-systolic volumes (contrast ventriculography), and (5) the clinical symptoms (Canadian Cardiovascular Society [CCS] anina score and New York Heart Association [NYHA] functional class) at follow-up. Three hundred sixty patients are randomly assigned into 1 of 4 groups: group A, early treatment (21-42 days after AMI) with intracoronary injection; group B, early treatment with combined application; group C, late treatment (3 months after AMI) with intracoronary delivery; and group D, late treatment with combined administration of BM-SCs. Besides the BM-SCs therapy, the standardized treatment of AMI is applied in all patients. CONCLUSIONS: The Myocardial Stem Cell Administration After Acute Myocardial Infarction Trial is the first randomized trial to investigate the effects of the combined (intramyocardial and intracoronary) and the intracoronary mode of delivery of BM-SCs therapy in the early and late periods after AMI.

Oguz, E., et al. (2011). "Long-term results of autologous stem cell transplantation in the treatment of patients with congestive heart failure." Transplant Proc **43**(3): 931-934.

BACKGROUND: The aim of this study was to assess the long-term efficacy of stem cell transplantation with revascularization for patients with ischemic cardiomyopathy. METHODS: We enrolled 17 patients with ischemic cardiomyopathy who had undergone autologous stem cell treatment. To assess myocardial ischemia and viability they underwent coronary angiography, stress tests with dobutamine, echocardiography, and positron emission tomography. Peripheral stem cells mobilized using granulocyte colony-stimulating factor (G-CSF) were collected by aphseresis for transplantation transmyocardially into the areas of injury during coronary artery bypass surgery to increase blood flow to the engrafted areas. RESULTS: Three patients died in the early follow-up period and 4 patients with cardiac failure died during mid-term follow-up; they all underwent stem cell transplantation at 6 months after acute myocardial infarction. The mean follow-up period of the remaining 10 patients was 85.8 +/- 9.2 months (range, 70-100). Mean left ventricular ejection fraction improved to 30.0 +/- 6.7, whereas the preoperative mean left ventricular ejection fraction of the surviving patients was 25.6 +/- 4.5 (P = .035). Mean New York Heart Association (NYHA) functional class decreased from 3.2 to 1.5 (P = .006). When the study population was divided into 2 subgroups according to the interval between acute myocardial infraction and surgery, the patients who underwent autologous stem cell transplantation within the first 6 months after myocardial infraction (Group 1) showed significantly lower NYHA scores at the last follow-up (P = .024 in Group 1 and P = .102 in Group 2). No side effects were observed to be due to the stem cell or G-CSF injections. CONCLUSION: Treatment of ischemic cardiomyopathy with autologous stem cell transplantation is easy and safe, opening a new window in the treatment of "no hope" patients.

Paitazoglou, C., et al. (2019). "Rationale and design of the European multicentre study on Stem Cell therapy in IschEmic Non-treatable Cardiac diseasE (SCIENCE)." Eur J Heart Fail **21**(8): 1032-1041.

AIMS: Ischaemic heart failure (IHF) patients have a poor prognosis even with current guideline-derived therapy. Intramyocardial injections of autologous or allogeneic mesenchymal stromal cells might improve cardiac function leading to better clinical outcome. METHODS: The SCIENCE (Stem Cell therapy in IschEmic Non-treatable Cardiac diseasE) consortium has initiated a Horizon 2020 funded multicentre phase II study in six European countries. It is a double-blind, placebo-controlled trial testing the safety and efficacy of allogeneic Cardiology Stem Cell Centre Adipose-derived Stromal Cells (CSCC_ASC) from healthy donors or placebo in 138 symptomatic IHF patients. Main inclusion criteria are New York Heart Association class II-III, left ventricular ejection fraction < 45% and N-terminal pro-B-type natriuretic peptide levels > 300 pg/mL. Patients are randomized in a 2:1 pattern to receive intramyocardial injections of either CSCC_ASC or placebo. CSCC_ASC and placebo treatments are prepared centralized at Rigshospitalet in 5 mL vials as an off-the-shelf product. Vials are distributed to all clinical partners and stored in nitrogen vapour tanks ready to be used directly after thawing. A total of 100 x 10(6) CSCC_ASC or placebo are injected directly into viable myocardium in the infarct border zone using the NOGA XP system (BDS, Cordis, Johnson & Johnson, USA). Primary endpoint is a centralized core-laboratory assessed change in left ventricular end-systolic volume at 6-month follow-up measured by echocardiography. The trial started in January 2017, 58 patients were included and treated until July 2018. CONCLUSION: The SCIENCE trial will provide clinical data on efficacy and safety of intramyocardial cell therapy of allogeneic adipose-derived stromal cells from healthy donors in patients with IHF.

Pandya, S. K. (2016). "Guidelines for stem cell science and clinical translation." Indian J Med Ethics **1**(3): 160-161.

The International Society for Stem Cell Research has released its updated guidelines for stem cell research in order to provide "assurance that stem cell research is conducted with scientific and ethical integrity and that new therapies are evidence-based." The guidelines were updated by a Guidelines Update Task Force consisting of twenty-five scientists, ethicists and experts in health care policy from nine countries. The chairpersons of this task force are Jonathan Kimmelman, George Daley and Insoo Hyun. There is no representative from India; the only person of Indian origin on it, Mahendra Rao, represents The New York Stem Cell Foundation.

Patel, K., et al. (2016). "Comparison of Subcutaneous versus Intravenous Alemtuzumab for Graft-versus-Host Disease Prophylaxis with Fludarabine/Melphalan-Based Conditioning in Matched Unrelated Donor Allogeneic Stem Cell Transplantation." Biol Blood Marrow Transplant **22**(3): 456-461.

The objective of this study was to compare infusion-related reactions and outcomes of using subcutaneous (subQ) alemtuzumab versus intravenous (i.v.) alemtuzumab as graft-versus-host disease (GVHD) prophylaxis for matched unrelated donor stem cell transplantations. Outcomes include incidence of cytomegalovirus (CMV)/Epstein-Barr (EBV) viremia, development of CMV disease or post-transplantation lymphoproliferative disorder, fatal infections, acute and chronic GVHD, time to engraftment, relapse rate, and survival. We conducted a retrospective study of all adult matched unrelated donor stem cell transplantations patients who received fludarabine/melphalan with subQ or i.v. alemtuzumab in combination with tacrolimus as part of their conditioning for unrelated donor transplantation at New York-Presbyterian/Weill Cornell Medical Center from January 1, 2012 to March 21, 2014. Alemtuzumab was administered at a total cumulative dose of 100 mg (divided over days -7 to -3). Forty-six patients received an unrelated donor stem cell transplantation with fludarabine/melphalan and either subQ (n = 26) or i.v. (n = 20) alemtuzumab in combination with tacrolimus. Within the evaluable population, 130 subQ and 100 i.v. alemtuzumab doses were administered. For the primary outcome, >/=grade 2 infusion-related reactions occurred in 11 (8%) versus 25 (25%) infusions in the subQ and i.v. cohorts, respectively (P = .001). Overall, 12 injections (9%) in the subQ arm versus 26 infusions (26%) in the i.v. arm experienced an infusion-related reaction of any grade (P = .001). There were no significant differences between the subQ and i.v. arms in rates of reactivation of CMV/EBV, development of CMV disease or post-transplantation lymphoproliferative disorder, fatal infections, acute and chronic GVHD, relapse, or survival. Subcutaneous administration of alemtuzumab for GVHD prophylaxis was associated with fewer infusion-related reactions compared with i.v. administration in the SCT setting. Incidences of acute and chronic GVHD were similar between both arms. There was also no difference in reactivation of CMV/EBV viremia, development of CMV disease or post-transplantation lymphoproliferative disorder, fatal infections, relapse, or survival.

Pham, H. P., et al. (2012). "Granulocyte transfusion therapy in pediatric patients after hematopoietic stem cell transplantation: a 5-year single tertiary care center experience." J Pediatr Hematol Oncol **34**(8): e332-336.

BACKGROUND: Granulocyte transfusion (GTx) has been used in neutropenic patients to treat infections; however, there are few studies that document its efficacy, especially in pediatric patients after hematopoietic stem cell transplantation (HSCT). We, therefore, reviewed the use of GTx in these patients. MATERIALS AND METHODS: A retrospective observational analysis was performed on all pediatric HSCT patients between January 2005 and January 2010 who met our institution's criteria for GTx and received more than 1 GTx. Unstimulated granulocyte donors were used until June 2007, followed by dexamethasone-stimulated donors thereafter. Outcomes were infection clearance, safety profile of GTx, and 30-day survival. RESULTS: One hundred fifty-three GTxs were administered to 16 pediatric HSCT patients. Indications for GTx: bacterial (69%), fungal (19%), and combined infection (12%). Concurrent infections, mostly bacterial, developed in 60% patients. One adverse reaction (pulmonary toxicity) was reported. The absolute neutrophil count of the stimulated products was significantly higher compared with the unstimulated products; however, neither the average number of granulocytes transfused by weight nor outcomes difference was noticed between these groups. CONCLUSIONS: GTx is safe in neutropenic and infected pediatric patients after HSCT. However, no difference in the outcomes was noticed between the group that received stimulated products and the group that received unstimulated products.

Phillips, A. A., et al. (2009). "A multi-institutional experience of autologous stem cell transplantation in North American patients with human T-cell lymphotropic virus type-1 adult T-cell leukemia/lymphoma suggests ineffective salvage of relapsed patients." Leuk Lymphoma **50**(6): 1039-1042.

Seo, S. K., et al. (2014). "Impact of peri-transplant vancomycin and fluoroquinolone administration on rates of bacteremia in allogeneic hematopoietic stem

cell transplant (HSCT) recipients: a 12-year single institution study." J Infect **69**(4): 341-351.

BACKGROUND: We analyzed the effect of peri-transplant prophylaxis on the epidemiology of bacteremia in a 12-year contemporary cohort of allogeneic HSCT recipients at our center. METHODS: This was an observational study of 1052 consecutive adult HSCT from 2000 to 2011. Formal prophylaxis with vancomycin only, fluoroquinolone (FQ) only, or vancomycin + FQ was implemented in 2006. The cumulative incidence of day 100 bacteremia was compared between the Early Period (2000-2005) and the Recent Period (2006-2011). Predictors for pre-engraftment bacteremia were analyzed with Cox-proportional hazard models in a subcohort of 821 HSCT who received myeloablative or reduced intensity conditioning (MA/RIC). RESULTS: The incidence of bacteremia decreased in the Recent Period (32% vs 27%; P = 0.002), whereas the rates of resistance in gram-negative rods (GNR) and vancomycin-resistant enterococci (VRE) were similar between the two Periods (P values are not statistically significant.) In multivariate analyses, prophylaxis with vancomycin only or vancomycin + FQ was protective (HR = 0.5; CI = 0.30-0.72) and (HR = 0.3; CI = 0.12-0.52, P < 0.01). Vancomycin or vancomycin + FQ eliminated viridans streptococcal bacteremia (VSB); vancomycin + FQ decreased GNR bacteremia (HR = 0.35; CI = 0.15-0.85). CONCLUSIONS: Vancomycin-based prophylaxis peri-transplant in MA/RIC HSCT was associated with elimination of VSB and may be considered at centers with high incidence of this infection.

Sleiman, Y., et al. (2020). "Modeling polymorphic ventricular tachycardia at rest using patient-specific induced pluripotent stem cell-derived cardiomyocytes." EBioMedicine **60**: 103024.

BACKGROUND: While mutations in the cardiac type 2 ryanodine receptor (RyR2) have been linked to exercise-induced or catecholaminergic polymorphic ventricular tachycardia (CPVT), its association with polymorphic ventricular tachycardia (PMVT) occurring at rest is unclear. We aimed at constructing a patient-specific human-induced pluripotent stem cell (hiPSC) model of PMVT occurring at rest linked to a single point mutation in RyR2. METHODS: Blood samples were obtained from a patient with PMVT at rest due to a heterozygous RyR2-H29D mutation. Patient-specific hiPSCs were generated from the blood samples, and the hiPSC-derived cardiomyocytes (CMs) were generated via directed differentiation. Using CRIPSR/Cas9 technology, isogenic controls were generated by correcting the RyR2-H29D mutation. Using patch-clamp, fluorescent confocal microscopy and video-image-based analysis, the molecular and functional properties of RyR2-H29D hiPSCCMs and control hiPSCCMs were compared. FINDINGS: RyR2-H29D hiPSCCMs exhibit intracellular sarcoplasmic reticulum (SR) Ca(2+) leak through RyR2 under physiological pacing. RyR2-H29D enhances the contribution of inositol 1,4,5-trisphosphate receptors to excitation-contraction coupling (ECC) that exacerbates abnormal Ca(2+) release in RyR2-H29D hiPSCCMs. RyR2-H29D hiPSCCMs exhibit shorter action potentials, delayed afterdepolarizations, arrhythmias and aberrant contractile properties compared to isogenic controls. The RyR2-H29D mutation causes post-translational remodeling that is fully reversed with isogenic controls. INTERPRETATION: To conclude, in a model based on a RyR2 point mutation that is associated with short-coupled PMVT at rest, RyR2-H29D hiPSCCMs exhibited aberrant intracellular Ca(2+) homeostasis, shortened action potentials, arrhythmias and abnormal contractile properties. FUNDING: French Muscular Dystrophy Association (AFM; project 16,073, MNM2 2012 and 20,225), "Fondation de la Recherche Medicale" (FRM; SPF20130526710), "Institut National pour la Sante et la Recherche Medicale" (INSERM), National Institutes of Health (ARM; R01 HL145473) and New York State Department of Health (NYSTEM C029156).

Son, T., et al. (2018). "Adaptation of Coping Together - a self-directed coping skills intervention for patients and caregivers in an outpatient hematopoietic stem cell transplantation setting: a study protocol." BMC Health Serv Res **18**(1): 669.

BACKGROUND: Despite numerous reports of significant distress and burden for hematopoietic stem cell transplantation (HSCT) patients and caregivers (CGs), HSCT-specific coping interventions remain rare. The few in use lack specificity and are often not easily accessible or cost-effective. Whereas the development of new interventions is resource-intensive, theory-informed adaptation of existing evidence-based interventions is promising. To date, no HSCT-specific intervention has relied on a formal adaptation approach. METHODS: Using the Center for Disease Control and Prevention's Map of Adaptation, this two-phase qualitative descriptive study seeks to understand the perceptions of HSCT patients, CGs, individually, and in dyads, and clinicians about Coping Together (CT) for the preliminary adaptation (Phase 1), and then explores perceptions of the modified intervention in additional mixed sample (Phase 2). Six to ten participants including outpatients, CGs and dyads and five to seven HSCT clinician participants will be recruited for Phase 1. For Phase 2, 14 to 16 participants including outpatients, CGs and dyads will be recruited. Individual and dyadic semi-structured

interviews will take place between 100 and 130 days post-HSCT. Verbatim transcripts will be analyzed using content analysis. DISCUSSION: It is paramount to have HSCT-specific supportive interventions that address patients' and CGs' multidimensional and complex needs. The timely involvement of key stakeholders throughout the adaptation process is likely to optimize the relevance and uptake of such tailored intervention. TRIAL REGISTRATION: This study is registered on October 6, 2016 in ClinicalTrials.gov at (identifier number NCT02928185).

Stadtmauer, E. A., et al. (2019). "Long-term safety and activity of NY-ESO-1 SPEAR T cells after autologous stem cell transplant for myeloma." Blood Adv **3**(13): 2022-2034.

This study in patients with relapsed, refractory, or high-risk multiple myeloma (MM) evaluated the safety and activity of autologous T cells engineered to express an affinity-enhanced T-cell receptor (TCR) that recognizes a peptide shared by cancer antigens New York esophageal squamous cell carcinoma-1 (NY-ESO-1) and L-antigen family member 1 (LAGE-1) and presented by HLA-A*02:01. T cells collected from 25 HLA-A*02:01-positive patients with MM expressing NY-ESO-1 and/or LAGE-1 were activated, transduced with self-inactivating lentiviral vector encoding the NY-ESO-1(c259)TCR, and expanded in culture. After myeloablation and autologous stem cell transplant (ASCT), all 25 patients received an infusion of up to 1 x 10(10) NY-ESO-1 specific peptide enhanced affinity receptor (SPEAR) T cells. Objective response rate (International Myeloma Working Group consensus criteria) was 80% at day 42 (95% confidence interval [CI], 0.59-0.93), 76% at day 100 (95% CI, 0.55-0.91), and 44% at 1 year (95% CI, 0.24-0.65). At year 1, 13/25 patients were disease progression-free (52%); 11 were responders (1 stringent complete response, 1 complete response, 8 very good partial response, 1 partial response). Three patients remained disease progression-free at 38.6, 59.2, and 60.6 months post-NY-ESO-1 SPEAR T-cell infusion. Median progression-free survival was 13.5 months (range, 3.2-60.6 months); median overall survival was 35.1 months (range, 6.4-66.7 months). Infusions were well tolerated; cytokine release syndrome was not reported. No fatal serious adverse events occurred during study conduct. NY-ESO-1 SPEAR T cells expanded in vivo, trafficked to bone marrow, demonstrated persistence, and exhibited tumor antigen-directed functionality. In this MM patient population, NY-ESO-1 SPEAR T-cell therapy in the context of ASCT was associated with antitumor activity. This trial was registered at www.clinicaltrials.gov as #NCT01352286.

Stefanantoni, K., et al. (2015). "Elevated serum levels of macrophage migration inhibitory factor and stem cell growth factor beta in patients with idiopathic and systemic sclerosis associated pulmonary arterial hypertension." Reumatismo **66**(4): 270-276.

Pulmonary arterial hypertension (PAH) can be idiopathic or secondary to autoimmune diseases, and it represents one of the most threatening complications of systemic sclerosis (SSc). Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine with proinflammatory functions that appears to be involved in the pathogenesis of hypoxia-induced PH. In SSc patients, high serum levels of MIF have been associated with the development of ulcers and PAH. Stem cell growth factor beta (SCGF beta) is a human growth factor that, together with MIF, is involved in the pathogenesis of chronic spinal cord injury. The aim of our study was to measure serum levels of MIF in patients with idiopathic and SSc-associated PAH. We enrolled 13 patients with idiopathic PAH and 15 with SSc-associated PAH. We also selected 14 SSc patients without PAH and 12 normal healthy controls, matched for sex and age. PAH was confirmed by right hearth catheterism (mPAP>25 mmHg). MIF and SCGF beta levels were measured by ELISA. We found significantly higher circulating levels of MIF and of SCGF beta in patients with idiopathic PAH (P=0.03 and P=0.004) and with PAH secondary to SSc (P=0.018 and P=0.023) compared to SSc patients without PAH. Higher levels of MIF were found in those patients with an higher New York Heart Association (NYHA) class (P=0.03). We can hypothesize that MIF and SCGF beta are able to play a role in PAH, both idiopathic or secondary, and in the future they may be evaluated as useful biomarkers and prognostic factors for this serious vascular disease.

Stefanova, V. T., et al. (2012). "Derivation of novel genetically diverse human embryonic stem cell lines." Stem Cells Dev **21**(9): 1559-1570.

Human embryonic stem cells (hESCs) have the potential to revolutionize many biomedical fields ranging from basic research to disease modeling, regenerative medicine, drug discovery, and toxicity testing. A multitude of hESC lines have been derived worldwide since the first 5 lines by Thomson et al. 13 years ago, but many of these are poorly characterized, unavailable, or do not represent desired traits, thus making them unsuitable for application purposes. In order to provide the scientific community with better options, we have derived 12 new hESC lines at New York University from discarded genetically normal and abnormal embryos using the latest techniques. We examined the genetic status of the NYUES lines in detail as well as their molecular and cellular features and DNA fingerprinting profile. Furthermore, we

differentiated our hESCs into the tissues most affected by a specific condition or into clinically desired cell types. To our knowledge, a number of characteristics of our hESCs have not been previously reported, for example, mutation for alpha thalassemia X-linked mental retardation syndrome, linkage to conditions with a genetic component such as asthma or poor sperm morphology, and novel combinations of ethnic backgrounds. Importantly, all of our undifferentiated euploid female lines tested to date did not show X chromosome inactivation, believed to result in superior potency. We continue to derive new hESC lines and add them to the NIH registry and other registries. This should facilitate the use of our hESCs and lead to advancements for patient-benefitting applications.

Strauer, B. E. and G. Steinhoff (2011). "10 years of intracoronary and intramyocardial bone marrow stem cell therapy of the heart: from the methodological origin to clinical practice." J Am Coll Cardiol **58**(11): 1095-1104.

Intracoronary and intramyocardial stem cell therapy aim at the repair of compromised myocardium thereby--as a causal treatment--preventing ventricular remodeling and improving overall performance. Since the first-in-human use of bone marrow stem cells (BMCs) after acute myocardial infarction in 2001, a large number of clinical studies have demonstrated their clinical benefit: BMC therapy can be performed with usual cardiac catheterization techniques in the conscious patient as well as also easily during cardiosurgical interventions. New York Heart Association severity degree of patients as well as physical activity improve in addition to ("on top" of) all other therapeutic regimens. Stem cell therapy also represents an ultimate approach in advanced cardiac failure. For acute myocardial infarction and chronic ischemia, long-term mortality after 1 and 5 years, respectively, is significantly reduced. A few studies also indicate beneficial effects for chronic dilated cardiomyopathy. The clinical use of autologous BMC therapy implies no ethical problems, when unmodified primary cells are used. With the use of primary BMCs, there are no major stem cell-related side effects, especially no cardiac arrhythmias and inflammation. Various mechanisms of the stem cell action in the human heart are discussed, for example, cell transdifferentiation, cell fusion, activation of intrinsic cardiac stem cells, and cytokine-mediated effects. New techniques allow point-of-care cell preparations, for example, within the cardiac intervention or operation theater, thereby providing short preparation time, facilitated logistics of cell transport, and reasonable cost effectiveness of the whole procedure. The 3 main indications are acute infarction, chronic ischemic heart failure, and dilated cardiomyopathy. Future studies are desirable to further elucidate the mechanisms of stem cell action and to extend the current use of intracoronary and/or intramyocardial stem cell therapy by larger and presumably multicenter and randomized trials.

Thies, R. S. and C. E. Murry (2015). "The advancement of human pluripotent stem cell-derived therapies into the clinic." Development **142**(20): 3614.

There was an error published in Development 142, 3077-3084.On p. 3081, it was incorrectly stated that Dr Lorenz Studer's group is supported by the New York Stem Cell Foundation. The correct funding credit is the New York State Stem Cell Science program.The authors apologise to readers for this mistake.

Tompkins, B. A., et al. (2018). "Comparison of Mesenchymal Stem Cell Efficacy in Ischemic Versus Nonischemic Dilated Cardiomyopathy." J Am Heart Assoc **7**(14).

BACKGROUND: Ischemic cardiomyopathy (ICM) and dilated cardiomyopathy (DCM) differ in histopathology and prognosis. Although transendocardial delivery of mesenchymal stem cells is safe and provides cardiovascular benefits in both, a comparison of mesenchymal stem cell efficacy in ICM versus DCM has not been done. METHODS AND RESULTS: We conducted a subanalysis of 3 single-center, randomized, and blinded clinical trials: (1) TAC-HFT (Transendocardial Autologous Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells in Ischemic Heart Failure Trial); (2) POSEIDON (A Phase I/II, Randomized Pilot Study of the Comparative Safety and Efficacy of Transendocardial Injection of Autologous Mesenchymal Stem Cells Versus Allogeneic Mesenchymal Stem Cells in Patients With Chronic Ischemic Left Ventricular Dysfunction Secondary to Myocardial Infarction); and (3) POSEIDON-DCM (Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis in Dilated Cardiomyopathy). Baseline and 1-year cardiac structure and function and quality-of-life data were compared in a post hoc pooled analysis including ICM (n=46) and DCM (n=33) patients who received autologous or allogeneic mesenchymal stem cells. Ejection fraction improved in DCM by 7% (within-group, P=0.002) compared to ICM (1.5%; within-group, P=0.14; between-group, P=0.003). Similarly, stroke volume increased in DCM by 10.59 mL (P=0.046) versus ICM (-0.2 mL; P=0.73; between-group, P=0.02). End-diastolic volume improved only in ICM (10.6 mL; P=0.04) and end-systolic volume improved only in DCM (17.8 mL; P=0.049). The sphericity index decreased only in ICM (-0.04; P=0.0002). End-diastolic mass increased in ICM (23.1 g; P<0.0001) versus DCM (-4.1 g; P=0.34;

between-group, P=0.007). The 6-minute walk test improved in DCM (31.1 m; P=0.009) and ICM (36.3 m; P=0.006) with no between-group difference (P=0.79). The New York Heart Association class improved in DCM (P=0.005) and ICM (P=0.02; between-group P=0.20). The Minnesota Living with Heart Failure Questionnaire improved in DCM (-19.5; P=0.002) and ICM (-6.4; P=0.03; delta between-group difference P=0.042) patients. CONCLUSIONS: Mesenchymal stem cell therapy is beneficial in DCM and ICM patients, despite variable effects on cardiac phenotypic outcomes. Whereas cardiac function improved preferentially in DCM patients, ICM patients experienced reverse remodeling. Mesenchymal stem cell therapy enhanced quality of life and functional capacity in both etiologies. CLINICAL TRIAL REGISTRATION: URL: http://www.clinicaltrials.gov. Unique identifiers: TAC-HFT: NCT00768066, POSEIDON: NCT01087996, POSEIDON-DCM: NCT01392625.

Waheed, F., et al. (2004). "High dose chemotherapy with thiotepa, mitoxantrone and carboplatin (TMJ) followed by autologous stem cell support in 100 consecutive lymphoma patients in a single centre: analysis of efficacy, toxicity and prognostic factors." Leuk Lymphoma **45**(11): 2253-2259.

High dose chemotherapy with autologous stem cell transplant is often used in patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) who either do not respond to, or relapse after conventional chemotherapy. There is no consensus on the "ideal" pretransplant conditioning regimen. In this study, we analyzed the results of 100 consecutive patients with HD and NHL who met our eligibility criteria and underwent autologous stem cell transplant at New York Medical College and Zalmen A. Arlin Cancer Institute. All patients received high dose chemotherapy with thiotepa, mitoxantrone and carboplatin (TMJ). One hundred patients, 37 with HD and 63 with NHL underwent autologous stem cell transplant using TMJ as a conditioning regimen. All patients with HD had chemo-sensitive relapse while 50 patients with NHL had chemo-sensitive relapse and 13 patients had first complete remission. The source of stem cells was bone marrow (18 patients), peripheral blood (50 patients) and both bone marrow and peripheral blood (32 patients). With a median follow up of 91 months (range 23-147 months), the median survival of patients with HD and NHL who underwent autologous stem cell transplant is 107 months and the 5 years disease free survival is 43%. Median survival of patients with HD and NHL is 87 and 107 months respectively. There were 4 transplant related deaths. Median survival of patients who had sensitive relapse at the time of transplant is 87 months while median survival has not been reached for patients who had first complete remission at the time of transplant. Multivariate analysis identified age>35 years (P=0.02) as a predictor for poor survival for the whole group as well as for patients with NHL (P=0.04). TMJ is a safe and effective regimen when used as a part of autologous stem cell transplant for patients with HD and NHL.

Wang, Y., et al. (2019). "Effect of stem cell transplantation on patients with ischemic heart failure: a systematic review and meta-analysis of randomized controlled trials." Stem Cell Res Ther **10**(1): 125.

Stem cell transplantation (SCT) has become a promising way to treat ischemic heart failure (IHF). We performed a large-scale meta-analysis of randomized clinical trials to investigate the efficacy and safety of SCT in IHF patients. Randomized controlled trials (RCTs) involving stem cell transplantation for the treatment of IHF were identified by searching the PubMed, EMBASE, SpringerLink, Web of Science, and Cochrane Systematic Review databases as well as from reviews and the reference lists of relevant articles. Fourteen eligible randomized controlled trials were included in this study, for a total of 669 IHF patients, of which 380 patients were treated with SCT. The weighted mean difference (WMD) was calculated for changes in the New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV), and Canadian Cardiovascular Society (CCS) angina grade using a fixed effects model, while relative risk (RR) was used for mortality. Compared with the control group, SCT significantly lowered the NYHA class (MD = - 0.73, 95% CI - 1.32 to - 0.14, $P < 0.05$), LVESV (MD = - 14.80, 95% CI - 20.88 to - 8.73, $P < 0.05$), and CCS grade (MD = - 0.81, 95% CI - 1.45 to - 0.17, $P < 0.05$). Additionally, SCT increased LVEF (MD = 6.55, 95% CI 5.93 to 7.16, $P < 0.05$). However, LVEDV (MD = - 0.33, 95% CI - 1.09 to 0.44, $P > 0.05$) and mortality (RR = 0.86, 95% CI 0.45 to 1.66, $P > 0.05$) did not differ between the two groups. This meta-analysis suggests that SCT may contribute to the improvement of LVEF, as well as the reduction of the NYHA class, CCS grade, and LVESV. In addition, SCT does not affect mortality.

Weber, D., et al. (2017). "Microbiota Disruption Induced by Early Use of Broad-Spectrum Antibiotics Is an Independent Risk Factor of Outcome after Allogeneic Stem Cell Transplantation." Biol Blood Marrow Transplant **23**(5): 845-852.

In allogeneic stem cell transplantation (ASCT), systemic broad-spectrum antibiotics are frequently used for treatment of infectious complications, but their

effect on microbiota composition is still poorly understood. This retrospective analysis of 621 patients who underwent ASCT at the University Medical Center of Regensburg and Memorial Sloan Kettering Cancer Center in New York assessed the impact of timing of peritransplant antibiotic treatment on intestinal microbiota composition as well as transplant-related mortality (TRM) and overall survival. Early exposure to antibiotics was associated with lower urinary 3-indoxyl sulfate levels (P < .001) and a decrease in fecal abundance of commensal Clostridiales (P = .03) compared with late antibiotic treatment, which was particularly significant (P = .005) for Clostridium cluster XIVa in the Regensburg group. Earlier antibiotic treatment before ASCT was further associated with a higher TRM (34%, 79/236) compared with post-ASCT (21%, 62/297, P = .001) or no antibiotics (7%, 6/88, P < .001). Timing of antibiotic treatment was the dominant independent risk factor for TRM (HR, 2.0; P </= .001) in multivariate analysis besides increase age (HR, 2.15; P = .004), reduced Karnofsky performance status (HR, 1.47; P = .03), and female donor-male recipient sex combination (HR, 1.56; P = .02) A competing risk analysis revealed the independent effect of early initiation of antibiotics on graft-versus-host disease-related TRM (P = .004) in contrast to infection-related TRM and relapse (not significant). The poor outcome associated with early administration of antibiotic therapy that is active against commensal organisms, and specifically the possibly protective Clostridiales, calls for the use of Clostridiales-sparing antibiotics and rapid restoration of microbiota diversity after cessation of antibiotic treatment.

Weinstock, D. M., et al. (2007). "Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant." Biol Blood Marrow Transplant **13**(5): 615-621.

Bloodstream infection caused by vancomycin-resistant enterococcus (VRE) is associated with very high mortality among allogeneic hematopoietic stem cell transplant (alloHSCT) recipients. However, it remains unclear whether VRE bloodstream infection directly causes mortality in the early posttransplant period or is simply a marker of poor outcome. To determine the risk factors for VRE bloodstream infection and its effect on outcome, we followed 92 patients screened for stool colonization by VRE upon admission for alloHSCT. Patient records were reviewed to determine outcomes, including mortality and microbiologic failure. Colonization by VRE was extremely common, occurring in 40.2% of patients. VRE bloodstream infection developed in 34.2% of colonized patients by day +35, compared to 1.8% without VRE colonization (P < .01). VRE bloodstream infection was associated with a significant decrement in survival and frequent microbiologic failure, despite treatment with linezolid and/or daptomycin. Five (35.7%) of 14 patients with VRE bloodstream infection had attributable mortality or contributing mortality from the infection. Strain typing by pulsed-field gel electrophoresis identified 9 different VRE strains among the 37 colonized patients and 5 patients with different strains recovered from the stool and the blood. In conclusion, stool screening effectively identified patients at extremely high risk for VRE bloodstream infection. The high mortality of VRE in the early posttransplant period supports the use of empiric antibiotics with activity against VRE during periods of fever and neutropenia in colonized patients.

Yerebakan, C., et al. (2011). "Impact of preoperative left ventricular function and time from infarction on the long-term benefits after intramyocardial CD133(+) bone marrow stem cell transplant." J Thorac Cardiovasc Surg **142**(6): 1530-1539 e1533.

OBJECTIVE: Our objective was to elucidate long-term clinical and functional effects of intramyocardial stem cell transplant and to identify patients who will show sustained benefit. METHODS: Long-term outcomes of 35 patients after intramyocardial CD133(+) bone marrow stem cell transplant during coronary artery bypass grafting were compared with those of a control group of 20 patients after coronary artery bypass grafting alone. Clinical effects were assessed with the New York Heart Association classification system and the Minnesota Living With Heart Failure questionnaire. Electrocardiography, 24-hour Holter monitoring, echocardiography, myocardial perfusion scanning, magnetic resonance imaging, and computed tomography were performed. Logistic regression analyses were used to identify prognostic factors for improvement in long-term left ventricular ejection fraction after stem cell treatment. RESULTS: The stem cell group revealed similar New York Heart Association and life quality scores to the control group. Myocardial perfusion score at the area of risk was significantly increased in the stem cell group after 36-month follow-up (P = .024 vs control). Multivariate logistic regression analysis revealed a 44-fold higher probability of at least 5% improvement in left ventricular ejection fraction for patients with preoperative left ventricular ejection fraction not greater than 40% than for patients with preoperative ejection fraction greater than 40% (P = .018). Furthermore, patients operated on between 7 and 12 weeks after myocardial infarction had a 56-fold higher chance of at least 5% improvement in left ventricular ejection fraction than patients treated later than 12

weeks after infarction (P = .023). CONCLUSIONS: Intramyocardial stem cell therapy was safe but lacked significant lasting benefits beyond 6 months in our study cohort with a limited number of patients. Preoperative left ventricular ejection fraction and time since myocardial infarction may be critical parameters for selection of patients who can benefit most from intramyocardial stem cell treatment during coronary artery bypass grafting.

Zhao, F., et al. (2017). "Effective tumor immunity to melanoma mediated by B16F10 cancer stem cell vaccine." Int Immunopharmacol **52**: 238-244.

Although tumor vaccines have been considered a promising immunotherapy approach, therapeutic tumor vaccines are mostly disappointing in the clinic due to vaccine weak immunogenicity. Cancer stem cells (CSCs) may broaden the antigenic breadth and effectively induce the immune responses against autologous cancer cells. Here we report on the development of the B16F10 CD133(+)CD44(+)CSCs (B16F10 CSCs) vaccine to induce tumor immunity to melanoma in mice. Efficacy of against melanoma was evaluated by analysis of tumor growth and mouse survival. Immunogenicity was assessed by ELISA and flow cytometric assays, including serum cytokines, cytotoxic activity of NK cells and splenocytes in the immunized mice. The results showed that the B16F10 CSC vaccine resulted in tumor shrinkage and mouse lifespan extension. The cytotoxic activity and IFN-gamma level were significantly increased in mice immunized with B16F10 CSC vaccine compared with the mice immunized with control vaccines. Additionally, New York esophageal squamous cell carcinoma-1, an efficient tumor associated antigen over-expressed by B16F10 CSCs, was markedly reduced in expression in melanoma tissue, suggesting decrease of CSC subpopulation due to B16F10 CSC vaccination. Collectively, the findings may represent a new powerful approach for treatment of melanoma by B16F10 CSC vaccination.

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