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Stem Cell

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Stem Cell Technology Research Literatures

Dr. Mark Herbert

World Development Institute
39-06 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

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.

Brennand, K. J. (2022). "Using Stem Cell Models to Explore the Genetics Underlying Psychiatric Disorders: Linking Risk Variants, Genes, and Biology in Brain Disease." Am J Psychiatry **179**(5): 322-328.

There is an urgent and unmet need to advance our ability to translate genetic studies of psychiatric disorders into clinically actionable information, which could transform diagnostics and even one day lead to novel (and potentially presymptomatic) therapeutic interventions. Today, although there are hundreds of significant loci associated with psychiatric disorders, resolving the target gene(s) and pathway(s) impacted by each is a major challenge. Integrating human induced pluripotent stem cell-based approaches with CRISPR-mediated genomic engineering strategies makes it possible to study the impact of patient-specific variants within the cell types of the brain. As the scale and scope of functional genomic studies expands, so does our ability to resolve the complex interplay of the many risk variants linked to psychiatric disorders. In this review, the author discusses some of the technological advances that make it possible to ask exciting questions that are fundamental to our understanding of psychiatric disorders. How do distinct risk variants converge and interact with each other (and the environment) across the diverse cell types that comprise the human brain? Can clinical trajectories and/or therapeutic response be predicted from genetic profiles? Just as critically, by spreading the message that genetic risk for psychiatric disorders is biological and fundamentally no different than for other human conditions, we can dispel the stigma associated with mental illness.

Brooks, D. L. and K. Musunuru (2021). "Detoxifying chemotherapy with genetics-guided stem cell modeling: A personalized affair." Cell Stem Cell **28**(12): 2039-2040.

Doxorubicin chemotherapy causes cardiotoxicity in some patients and spares others. In this issue of Cell Stem Cell, Magdy et al. (2021) use genome-edited iPSCs to establish a common RARG coding variant as a causal risk factor, pointing to a pharmacogenomic application and to RARG-targeting treatments to protect patients from cardiotoxicity.

Dickinson, A. M. (2007). "Risk assessment in haematopoietic stem cell transplantation: pre-transplant

patient and donor factors: non-HLA genetics." Best Pract Res Clin Haematol **20**(2): 189-207.

Non-HLA genetics involving the study of single-nucleotide polymorphisms (SNPs) and microsatellites of cytokine and cytokine receptor genes, and as well as genes associated with response to infection and therapeutic drugs, are currently being studied for associations with diseases, including autoimmune disease, cancer and solid-organ transplant rejection. This chapter will summarize the potential role of non-HLA genetics in predicting outcome of haematopoietic stem-cell transplantation (HSCT) and how genotyping for non-HLA genes may give insight into the immunobiology of HSCT complications, including GvHD and infectious episodes. Future directions - including the role of pharmacogenomics, use of the research results for individualized medicine, and interpretation of data - will also be discussed.

Esmail, S. and W. R. Danter (2021). "NEUBOrg: Artificially Induced Pluripotent Stem Cell-Derived Brain Organoid to Model and Study Genetics of Alzheimer's Disease Progression." Front Aging Neurosci **13**: 643889.

Alzheimer's disease (AD) is the most common type of neurodegenerative diseases. There are over 44 million people living with the disease worldwide. While there are currently no effective treatments for AD, induced pluripotent stem cell-derived brain organoids have the potential to provide a better understanding of Alzheimer's pathogenesis. Nevertheless, developing brain organoid models is expensive, time consuming and often does not reflect disease progression. Using accurate and inexpensive computer simulations of human brain organoids can overcome the current limitations. Induced whole brain organoids (aiWBO) will greatly expand our ability to model AD and can guide wet lab research. In this study, we have successfully developed and validated artificially induced a whole brain organoid platform (NEUBOrg) using our previously validated machine learning platform, DeepNEU (v6.1). Using NEUBorg platform, we have generated aiWBO simulations of AD and provided a novel approach to test genetic risk factors associated with AD progression and pathogenesis.

Greenspan, L. J., et al. (2015). "Genetics of gonadal stem cell renewal." Annu Rev Cell Dev Biol **31**: 291-315.

Stem cells are necessary for the maintenance of many adult tissues. Signals within the stem cell microenvironment, or niche, regulate the self-renewal and differentiation capability of these cells. Misregulation of these signals through mutation or damage can lead to overgrowth or depletion of different stem cell pools. In this review, we focus on the Drosophila testis and ovary, both of which contain well-defined niches, as well as the mouse testis, which has become a more approachable stem cell system with recent technical advances. We discuss the signals that regulate gonadal stem cells in their niches, how these signals mediate self-renewal and differentiation under homeostatic conditions, and how stress, whether from mutations or damage, can cause changes in cell fate and drive stem cell competition.

Grieshammer, U. and K. A. Shepard (2014). "Proceedings: consideration of genetics in the design of induced pluripotent stem cell-based models of complex disease." Stem Cells Transl Med **3**(11): 1253-1258.

The goal of exploiting induced pluripotent stem cell (iPSC) technology for the discovery of new mechanisms and treatments of disease is being pursued by many laboratories, and analyses of rare monogenic diseases have already provided ample evidence that this approach has merit. Considering the enormous medical burden imposed by common chronic diseases, successful implementation of iPSC-based models has the potential for major impact on these diseases as well. Since common diseases represent complex traits with varying genetic and environmental contributions to disease manifestation, the use of iPSC technology poses unique challenges. In this perspective, we will consider how the genetics of complex disease and mechanisms underlying phenotypic variation affect experimental design.

Julian, D., et al. (2019). "Convergence of human cellular models and genetics to study neural stem cell signaling to enhance central nervous system regeneration and repair." Semin Cell Dev Biol **95**: 84-92.

Human central nervous system (CNS) regeneration is considered the holy grail of neuroscience research, and is one of the most pressing and difficult questions in biology and science. Despite more than 20 years of work in the field of neural stem cells (NSCs), the area remains in its infancy as our understanding of the fundamental mechanisms that can be leveraged to improve CNS regeneration in neurological diseases is still growing. Here, we focus on the recent lessons from lower organism CNS regeneration genetics and how such findings are starting to illuminate our understanding of NSC signaling pathways in humans. These findings will allow us to improve upon our knowledge of endogenous NSC function, the utility of exogenous NSCs, and the limitations of NSCs as therapeutic vehicles for providing relief from devastating human neurological diseases. We also discuss the limitations of activating NSC signaling for CNS repair in humans, especially the potential for tumor formation. Finally, we will review the recent

advances in new culture techniques, including patient-derived cells and cerebral organoids to model the genetic regulation of signaling pathways controlling the function of NSCs during injury and disease states.

Kahn, J. P. and A. C. Mastroianni (2004). "Creating a stem cell donor: a case study in reproductive genetics." Kennedy Inst Ethics J **14**(1): 81-96.

During the nearly 10 years since its introduction, preimplantation genetic diagnosis (PGD) has been used predominantly to avoid giving birth to a child with identified genetic disease. Recently, PGD was used by a couple not only to test IVF-created embryos for genetic disease, but also to test for a nondisease trait related to immune compatibility with a child in the family in need of an hematropoetic stem cell transplant. This article describes the case, raises some ethical and policy issues, highlights gaps in U.S. policy, and finally makes some recommendations for addressing advancing genetic and reproductive technologies.

Kidson, S. H., et al. (2016). "The rise of developmental genetics - a historical account of the fusion of embryology and cell biology with human genetics and the emergence of the Stem Cell Initiative." S Afr Med J **106**(6 Suppl 1): S57-58.

Genetics and cell biology are very prominent areas of biological research with rapid advances being driven by a flood of theoretical, technological and informational knowledge. Big biology and small biology continue to feed off each other. In this paper, we provide a brief overview of the productive interactions that have taken place between human geneticists and cell biologists at UCT, and credit is given to the enabling environment created led by Prof. Peter Beighton. The growth of new disciplines and disciplinary mergers that have swept away division of the past to make new exciting syntheses are discussed. We show how our joint research has benefitted from worldwide advances in developmental genetics, cloning and stem cell technologies, genomics, bioinformatics and imaging. We conclude by describing the role of the UCT Stem Cell Initiative and show how we are using induced pluripotent cells to carry out disease-in-the- dish studies on retinal degeneration and fibrosis.

Kobbe, G., et al. (2019). "Molecular genetics in allogeneic blood stem cell transplantation for myelodysplastic syndromes." Expert Rev Hematol **12**(10): 821-831.

Introduction: Myelodysplastic Syndromes (MDS) are a heterogeneous group of myeloid neoplasms arising in a multipotent hematopoietic stem cell. In about 50% of cases, chromosomal aberrations are detected, which can serve as clonal markers as well as important prognostic factors. In recent years, many somatic mutations have been recognized to be involved in the initiation and clonal evolution of MDS. They provide prognostic information, not only regarding the natural course of disease but also regarding the outcome of allogeneic stem cell transplantation (aSCT) and can be used to monitor the depth of treatment response and enable early detection of relapse. Areas covered: The authors describe current methods for mutation detection in MDS and highlight their prognostic significance. In addition, the authors discuss whether molecular findings should influence the approach to aSCT and how they can be used for minimal residual disease (MRD) detection and guidance for preemptive treatment of relapse. Expert opinion: Molecular genetics give insight into the pathophysiology of MDS, provide prognostic information on the natural course of disease and help to predict the success of several therapeutic approaches including aSCT. MRD monitoring based on next-generation sequencing will soon become the standard of care to guide treatment before and after aSCT.

Kroger, N., et al. (2017). "Impact of Molecular Genetics on Outcome in Myelofibrosis Patients after Allogeneic Stem Cell Transplantation." Biol Blood Marrow Transplant **23**(7): 1095-1101.

Molecular genetics may influence outcome for patients with myelofibrosis. To determine the impact of molecular genetics on outcome after allogeneic stem cell transplantation, we screened 169 patients with primary myelofibrosis (n = 110), post-essential thrombocythemia/polycythemia vera myelofibrosis (n = 46), and myelofibrosis in transformation (n = 13) for mutations in 16 frequently mutated genes. The most frequent mutation was JAK2V617F (n = 101), followed by ASXL1 (n = 49), calreticulin (n = 34), SRSF2 (n = 16), TET2 (n = 10), U2AF1 (n = 11), EZH2 (n = 7), MPL (n = 6), IDH2 (n = 5), IDH1 (n = 4), and CBL (n = 1). The cumulative incidence of nonrelapse mortality (NRM) at 1 year was 21% and of relapse at 5 years 25%. The 5-year rates progression-free (PFS) and overall survival (OS) were and 56%, respectively. In a multivariate analysis CALR mutation was an independent factor for lower NRM (HR, .415; P = .05), improved PFS (HR, .393; P = .01), and OS (HR, .448; P = .03). ASXL1 and IDH2 mutations were independent risk factors for lower PFS (HR, 1.53 [P = .008], and HR, 5.451 [P = .002], respectively), whereas no impact was observed for "triple negative" patients. Molecular genetics, especially CALR, IDH2, and ASXL1 mutations, may thus be useful to predict outcome independently from known clinical risk factors after allogeneic stem cell transplantation for myelofibrosis.

Kuliev, A., et al. (2005). "Preimplantation genetics: Improving access to stem cell therapy." Ann N Y Acad Sci **1054**: 223-227.
There has been progress in the application of stem cell transplantation for treatment of an increasing number of severe congenital and acquired bone marrow disorders, currently restricted by the availability of human leukocyte antigen (HLA)-matched related donors. Preimplantation HLA typing has recently been introduced to improve the access to stem cell therapy for inherited bone marrow failures. Preimplantation genetic diagnosis (PGD) provides an option not only for avoiding an affected pregnancy with thalassemia and other inherited disorders but also for preselection of the HLA-compatible donors for affected siblings. Multiple short tandem repeat markers throughout the HLA region are applied for this purpose, allowing 100% accuracy of HLA typing, through picking up possible recombination in the HLA region, as well as the copy number of chromosome 6, which affect accuracy of preimplantation HLA typing. Present experience of preimplantation HLA typing includes preimplantation HLA typing in 180 cycles, 122 of which were done as part of PGD for Fanconi anemia, thalassemia, Wiscott-Aldrich syndrome, hyper-immunoglobulin M syndrome, hypohidrotic ectodermal dysplasia with immune deficiency, and X-linked adrenoleukodystrophy, and 58 for the sole purpose of HLA typing for leukemias and for aplastic and Diamond-Blackfan anemia. The applied method resulted in the accurate preselection and transfer of 100% HLA-matched embryos, yielding already three dozen clinical pregnancies and the birth of two dozen HLA-matched children to the siblings requiring stem cell transplantation. Successful therapy with HLA-matched stem cells, obtained from these PGD children, has been achieved already for Diamond-Blackfan anemia hypohidrotic ectodermal dysplasia with immune deficiency and thalassemia.

Maali, A., et al. (2021). "Induced pluripotent stem cell technology: trends in molecular biology, from genetics to epigenetics." Epigenomics **13**(8): 631-647.
Induced pluripotent stem cell (iPSC) technology, based on autologous cells' reprogramming to the embryonic state, is a new approach in regenerative medicine. Current advances in iPSC technology have opened up new avenues for multiple applications, from basic research to clinical therapy. Thus, conducting iPSC trials have attracted increasing attention and requires an extensive understanding of the molecular basis of iPSCs. Since iPSC reprogramming is based on the methods inducing the expression of specific genes involved in pluripotency states, it can be concluded that iPSC reprogramming is strongly influenced by epigenetics. In this study, we reviewed the molecular basis of reprogramming, including the reprogramming factors (OCT4, SOX2, KLF4, c-MYC, NANOG, ESRRB, LIN28 as well as their regulatory networks), applied vectors (retroviral vectors, adenoviral vectors, Sendaiviral vectors, episomal plasmids, piggyBac, simple vectors, etc.) and epigenetic modifications (miRNAs, histones and DNA methylation states) to provide a comprehensive guide for reprogramming studies.

Miller, A. and G. Van Zant (2006). "Advances in hematopoietic stem cell research through mouse genetics." Curr Opin Hematol **13**(4): 209-215.
PURPOSE OF REVIEW: Successful bone marrow transplantation involves migration of hematopoietic stem cells through the blood, entering the extravascular hematopoietic cords, lodging in the proper niche, and expanding and differentiating to produce large numbers of mature cells -- all without depletion of the stem cell pool. An additional variable in these processes is the age of both the donor bone marrow and the recipient. Basic stem cell biology and transplant biology aim to uncover the molecular mechanisms controlling these processes. RECENT FINDINGS: Mouse genetics is a frequently used tool that allows dissection of individual pathways that influence properties of hematopoietic stem cells. Recently, the conception of a niche has been expanded to include evidence for a vascular and an endosteal niche. Additionally, hematopoietic stem cell interactions within the niche have been further defined, documenting the importance of cell cycle, cell adhesion, response to cytokine stimulation and age-dependent functional changes. A new model for hematopoietic stem cell aging was proposed that supports the hypothesis that stem cell aging is at least partially due to an accumulation of DNA damage leading to exhaustion. SUMMARY: This review focuses on the last year's progress using mouse genetics as a tool to study intrinsic mechanisms of hematopoietic stem cell biology.

Musunuru, K. (2018). "Stem cell modeling of lipid genetics." Curr Opin Lipidol **29**(2): 151-155.
PURPOSE OF REVIEW: To summarize recent advances with respect to the use of human pluripotent stem cells to study the genetics of blood lipid traits. RECENT FINDINGS: Human pluripotent stem cell models have been used to elucidate the mechanisms by which genes contribute to dyslipidemia, to discover new lipid-related DNA variants and genes, and to perform drug screens. SUMMARY: In addition to enabling a better understanding of the genetic basis of lipid metabolism, human pluripotent stem cells are identifying potential therapeutic targets as well as potential therapies.

Naugler, C. T. (2010). "Population genetics of cancer cell clones: possible implications of cancer stem cells." Theor Biol Med Model **7**: 42.

BACKGROUND: The population dynamics of the various clones of cancer cells existing within a tumour is complex and still poorly understood. Cancer cell clones can be conceptualized as sympatric asexual species, and as such, the application of theoretical population genetics as it pertains to asexual species may provide additional insights. RESULTS: The number of generations of tumour cells within a cancer has been estimated at a minimum of 40, but high cancer cell mortality rates suggest that the number of cell generations may actually be in the hundreds. Such a large number of generations would easily allow natural selection to drive clonal evolution assuming that selective advantages of individual clones are within the range reported for free-living animal species. Tumour cell clonal evolution could also be driven by variation in the intrinsic rates of increase of different clones or by genetic drift. In every scenario examined, the presence of cancer stem cells would require lower selection pressure or less variation in intrinsic rates of increase. CONCLUSIONS: The presence of cancer stem cells may result in more rapid clonal evolution. Specific predictions from theoretical population genetics may lead to a greater understanding of this process.

Odenike, O., et al. (2015). "Myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms: an update on risk stratification, molecular genetics, and therapeutic approaches including allogeneic hematopoietic stem cell transplantation." Am Soc Clin Oncol Educ Book: e398-412.

Myelodysplastic syndromes are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, peripheral cytopenias, and a variable propensity for leukemic transformation. In recent years there has been an explosion of information on the molecular genetic changes underlying these disorders. This information has substantial prognostic implications, and the influence on therapeutic approaches and the treatment of patients is evolving. Allogeneic hematopoietic stem cell transplantation (alloSCT) is the only known cure for these diseases, but appropriate patient selection is of utmost importance from a risk-benefit perspective. This review focuses on the factors influencing risk stratification in MDS and optimal choice of front-line therapy in the current era, including the interplay of clinical factors and molecular genetic factors, and factors that determine eligibility for alloSCT. The myelodysplastic/myeloproliferative diseases also will be discussed, including the increasing effort to understand the molecular genetics and natural history of these disorders and treatment approaches.

Streeter, I., et al. (2017). "The human-induced pluripotent stem cell initiative-data resources for cellular genetics." Nucleic Acids Res **45**(D1): D691-D697.

The Human Induced Pluripotent Stem Cell Initiative (HipSci) isf establishing a large catalogue of human iPSC lines, arguably the most well characterized collection to date. The HipSci portal enables researchers to choose the right cell line for their experiment, and makes HipSci's rich catalogue of assay data easy to discover and reuse. Each cell line has genomic, transcriptomic, proteomic and cellular phenotyping data. Data are deposited in the appropriate EMBL-EBI archives, including the European Nucleotide Archive (ENA), European Genome-phenome Archive (EGA), ArrayExpress and PRoteomics IDEntifications (PRIDE) databases. The project will make 500 cell lines from healthy individuals, and from 150 patients with rare genetic diseases; these will be available through the European Collection of Authenticated Cell Cultures (ECACC). As of August 2016, 238 cell lines are available for purchase. Project data is presented through the HipSci data portal (http://www.hipsci.org/lines) and is downloadable from the associated FTP site (ftp://ftp.hipsci.ebi.ac.uk/vol1/ftp). The data portal presents a summary matrix of the HipSci cell lines, showing available data types. Each line has its own page containing descriptive metadata, quality information, and links to archived assay data. Analysis results are also available in a Track Hub, allowing visualization in the context of public genomic annotations (http://www.hipsci.org/data/trackhubs).

Vieira, J. M. and P. R. Riley (2013). "Chemical genetics and its potential in cardiac stem cell therapy." Br J Pharmacol **169**(2): 318-327.

Over the last decade or so, intensive research in cardiac stem cell biology has led to significant discoveries towards a potential therapy for cardiovascular disease; the main cause of morbidity and mortality in humans. The major goal within the field of cardiovascular regenerative medicine is to replace lost or damaged cardiac muscle and coronaries following ischaemic disease. At present, de novo cardiomyocytes can be generated either in vitro, for cell transplantation or disease modelling using directed differentiation of embryonic stem cells or induced pluripotent stem cells, or in vivo via direct reprogramming of resident adult cardiac fibroblast or ectopic stimulation of resident cardiac stem or progenitor cells. A major bottleneck with all of these approaches is the low efficiency of cardiomyocyte

differentiation alongside their relative functional immaturity. Chemical genetics, and the application of phenotypic screening with small molecule libraries, represent a means to enhance understanding of the molecular pathways controlling cardiovascular cell differentiation and, moreover, offer the potential for discovery of new drugs to invoke heart repair and regeneration. Here, we review the potential of chemical genetics in cardiac stem cell therapy, highlighting not only the major contributions to the field so far, but also the future challenges.

Vlastarakos, P. V., et al. (2008). "Novel approaches to treating sensorineural hearing loss. Auditory genetics and necessary factors for stem cell transplant." Med Sci Monit **14**(8): RA114-125.

Sensorineural hearing loss is a chronic disease, with a serious impact on human communication and quality of life. Exposure to various factors can lead to irreversible hearing impairment, as the auditory epithelium in humans comprises terminally differentiated cells. By contrast, the inner ear of lower vertebrates and invertebrates shows regenerative capacity. Efforts to regenerate the damaged human inner ear may involve renewed cell proliferation, or transplanting cells that can differentiate into sensory cells. Literature review. Animal studies, in vitro studies, retrospective-cohort studies, community-based case-controls, clinical guidelines, and review articles. Embryonic stem cells, inner ear stem cells, and stem cells from other tissues (i.e., neural tissue, hematopoietic system) may be candidates for restoring the auditory epithelium. Transcriptional regulation of p27kip1 is the primary determinant of terminal mitosis and the final number of postmitotic progenitors of hair and supporting cells. Basic helix-loop-helix transcription factor Math1 was found to be necessary and sufficient for the production of auditory hair cells. Notch signaling seems to play a major role in the regulation of Math1, through lateral inhibition. Brn3c, Gfi1, and Barhl1 are also specific transcription factors that have been implicated in hair cell maintenance and consequent survival. Evidence concerning development, maintenance, and regeneration of hair cells is still at an embryonic stage. Combined data, as attempted in the present study, will lead to a more successful management of deafness.

Wang, T., et al. (2021). "Allogeneic Hematopoietic Stem Cell Transplantation Improved Survival for Adult Core Binding Factor Acute Myelogenous Leukemia Patients with Intermediate- and Adverse-Risk Genetics in the 2017 European LeukemiaNet." Transplant Cell Ther **27**(2): 173 e171-173 e179.

The use of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for consolidation therapy in patients with core binding factor (CBF) acute myelogenous leukemia (AML) with intermediate- and adverse-risk genetics remains controversial. We retrospectively analyzed the clinical outcomes of 286 CBF-AML patients with intermediate- and adverse-risk genetics in first complete remission following consolidation with chemotherapy (n = 122), auto-HSCT (n = 27), or allo-HSCT (n = 137) between January 2009 and December 2018 at our center. Patients with allo-HSCT showed superior 5-year overall survival (OS; 74% versus 38% or 49%; P < .001) and progression-free survival (PFS; 74% versus 26% or 49%; P < .001) and lower cumulative incidence of relapse (CIR; 9% versus 69% or 31%; P < .001) compared with chemotherapy alone or auto-HSCT. In the allo-HSCT group, minimal residual disease (MRD) at the second and third months after allo-HSCT could predict relapse in t(8;21) patients (2 months: P(CIR) = .002; 3 months: P(CIR) < .001) but not in inv(16) patients. Moreover, positive MRD after 2 courses of consolidation chemotherapy before allo-HSCT was an independent risk factor for survival in CBF-AML patients with intermediate- and adverse-risk genetics, whereas haploidentical donor (haplo-) HSCT could overcome the adverse prognosis (5-year OS, 87%; 5-year PFS, 81%; 5-year CIR, 7%). Allo-HSCT could be the optimal first-line consolidation therapy for patients with intermediate- and adverse-risk genetics, and haplo-HSCT could improve survival for patients with positive MRD after 2 courses of consolidation chemotherapy.

Yasuda, E., et al. (2015). "Molecular Genetics and Metabolism Report Long-term follow-up of post hematopoietic stem cell transplantation for Hurler syndrome: clinical, biochemical, and pathological improvements." Mol Genet Metab Rep **2**: 65-76.

Mucopolysaccharidosis type I (MPS I; Hurler Syndrome) is a lysosomal storage disease caused by a deficiency of the enzyme alpha-L-iduronidase which affects multiple organs such as central nervous system (CNS), skeletal system, and physical appearance. Hematopoietic stem cell transplantation (HSCT) is recommended as a primary therapeutic option at an early stage of MPS I with a severe form to ameliorate CNS involvement; however, no description of pathological improvement in skeletal dysplasia has been investigated to date. We here report a 15-year-old male case with MPS I post-HSCT. This patient received successful HSCT at the age of 2 years and 1 month, followed for over 10 years. His activity of daily living including cognitive performance has been kept normal and the present height and weight are 162 cm and 55 kg. Bone deformity has been still developed, resulting in hemiepiphysiodesis of bilateral medial proximal tibia at 12 years of age and successive arthrodesis of thoraco-lumbar spine at 13 years of age;

however, skeletal histopathology from surgical remnants showed substantial improvement in bone lesion with markedly reduced occurrence and cell size of vacuolated cells. After a series of surgical procedures, he became ambulant and independent in daily activity. The levels of GAGs in blood were substantially reduced. In conclusion, this long-term post-HSCT observation should shed light on a new aspect of therapeutic effect associated with skeletal pathology and GAG levels as a biomarker, indicating that HSCT is a primary choice at an early stage for not only CNS but skeletal system in combination of appropriate surgical procedures.

Zhu, J., et al. (2020). "Influence of Germline Genetics on Tacrolimus Pharmacokinetics and Pharmacodynamics in Allogeneic Hematopoietic Stem Cell Transplant Patients." Int J Mol Sci **21**(3).

Tacrolimus exhibits high inter-patient pharmacokinetics (PK) variability, as well as a narrow therapeutic index, and therefore requires therapeutic drug monitoring. Germline mutations in cytochrome P450 isoforms 4 and 5 genes (CYP3A4/5) and the ATP-binding cassette B1 gene (ABCB1) may contribute to interindividual tacrolimus PK variability, which may impact clinical outcomes among allogeneic hematopoietic stem cell transplantation (HSCT) patients. In this study, 252 adult patients who received tacrolimus for acute graft versus host disease (aGVHD) prophylaxis after allogeneic HSCT were genotyped to evaluate if germline genetic variants associated with tacrolimus PK and pharmacodynamic (PD) variability. Significant associations were detected between germline variants in CYP3A4/5 and ABCB1 and PK endpoints (e.g., median steady-state tacrolimus concentrations and time to goal tacrolimus concentration). However, significant associations were not observed between CYP3A4/5 or ABCB1 germline variants and PD endpoints (e.g., aGVHD and treatment-emergent nephrotoxicity). Decreased age and CYP3A5*1/*1 genotype were independently associated with subtherapeutic tacrolimus trough concentrations while CYP3A5*1*3 or CYP3A5*3/*3 genotypes, myeloablative allogeneic HSCT conditioning regimen (MAC) and increased weight were independently associated with supratherapeutic tacrolimus trough concentrations. Future lines of prospective research inquiry are warranted to use both germline genetic and clinical data to develop precision dosing tools that will optimize both tacrolimus dosing and clinical outcomes among adult HSCT patients.

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