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EDITORIAL

Research Leads to Approved Therapies in the New Era of Living Medicine

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Dr. Jan Nolta, Editor of STEM CELLS, is the Director of the Stem Cell Program at UC Davis School of Medicine and directs the new Institute for Regenerative Cures. The UC Davis stem cell program has over 150 faculty members collaborating to work toward stem cell-related cures for a spectrum of diseases and injuries. Her group focuses on "bench to the bedside" research, and she has been involved in numerous clinical trials of gene and cell therapy. She is scientific director of the new Good Manufacturing Practice clean room facility at UC Davis, where stem cells of different types are being isolated or expanded for clinical trials.

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In 2017, the fields of cell therapy and gene therapy have seen the first products approved by the Food and Drug Administration and commercialized for insurance reimbursement. This marks a new shift in the era of "living medicines." The fields of stem cells, immunotherapy, gene therapy, and regenerative medicine are poised to change the face of health care. Immunotherapy is giving terminal cancer patients a second chance at life, gene therapy can cure rare diseases, and living stem cells are beginning to be prescribed for certain indications. Gene editing offers unprecedented opportunity to alter stem cell genomes to make lasting cures for monogenic disorders, including countless rare diseases. This changes the fields of medicine, nursing, and pharmacy, since the new generations of health care students will need to learn how to handle drugs that are not pills or liquids in a vial, but rather are living biological medicines. The new "living medicine" preparation and delivery will be performed by large teams of experts with different expertise and backgrounds, including those with cell biology and manufacturing knowledge, in addition to experts in medicine, surgery, imaging, monitoring, outcomes, health technology, and statistical analysis.

The common passion to treat a specific disease or disorder unites these interesting multifaceted teams, and each member brings a unique perspective to the group. It is important for members of these broad and committed groups to remember to always seek evidence-based solutions for developing novel treatments that have the best chance of impacting the disorder that they hope to cure. Publication of peer-reviewed "Proof-of-Concept" data in reputable journals accelerates progress toward cures by disseminating knowledge in an evidence-based manner.

Our "sister journals," STEM CELLS (www.Stemcells.Com, @StemCellsJournl) and STEM CELLS TRANSLATIONAL MEDICINE (SCTM) (www.StemCellsTM.com, @StemCellsTM), have continued to publish important articles in the field, submitted by talented authors and research teams who are pushing forward the frontiers of cell and gene therapy, stem cell biology, immunotherapy, and regenerative medicine. We are grateful to all of our outstanding authors who have contributed to the sister journals in 2017. I would like to specifically congratulate our authors who have contributed to the field of stem cell gene therapy [1–3] and those who have contributed to a better understanding of cancer stem cells and targeting them through immunotherapy, as detailed below.

Articles published in STEM CELLS in 2017 helped to unravel the intricacies of cancer stem cells, to better understand and target them. Advances were described in the understanding of glioblastoma [4, 5], skin cancer [6], uterine and ovarian cancer [7, 8], leukemia [9] and multiple myeloma [10], thyroid cancer [11], bone [12] breast [13, 14], and lung cancer [15], as well as liver, colon, and gastric cancer [16–20].

There was an interesting review on "the malignant hematopoietic stem cell niche" [21]. Other reports focused on different types of treatment for malignancies [22], including a review on "Emerging Drugs Targeting Epithelial Cancer Stem-Like Cells" [23] and another on "Emerging Principles from the Clinical Application of Chimeric Antigen Receptor T Cell Therapies for B Cell Malignancies" [24]. In 2017, to further aid in the understanding of targeting neoplastic cells, we published an excellent review on "how the tumor microenvironment protects cancer stem cells" [25].

Articles contributed also to a better understanding of the immune system and its development and function, potentially leading to improved knowledge on how to more successfully use cell therapy in the field of immunology [26–28]. A subset of our 2017 articles focused on immunology in the context of mesenchymal stem/stromal cells or similar cell types, either in the microenvironment or after transplantation [29–37]. Davies et al., in the LeBlanc laboratory, provided evidence that "mesenchymal stromal cell (MSC) derived soluble PD-1 ligands modulate the activation status and effector function of CD4+ T cells" [38].

Together, these articles focusing on the immune system, cancer stem cell properties,

and ways to target the cancer stem cells have helped move the field forward toward better cancer immunotherapies of the future.

In 2018, STEM CELLS will continue to focus primarily on the functional and mechanistic aspects of stem cell biology and the potential of different types of stem cells for therapeutic applications, and we will report key, well-controlled advances in stem cell clinical trials. Articles should have definitive conclusions and be mechanism-based to be considered for potential publication in STEM CELLS. Our sister journal [39] SCTM provides an excellent forum for translational, clinical, and technical advances for stem cell therapy development. SCTM primarily covers technical advances in delivering cell therapy, advances in animal models, and new findings that help advance promising stem cell therapies closer to the clinic. We truly appreciate the associate editors, staff members, and authors who all contribute to the ability of both journals to publish the best stem cell articles.

I would also like to personally thank our outstanding reviewers, who have taken their precious time to referee articles for the journal. We rely upon their knowledge, expertise, fairness, skills, and insight to review the excellent papers submitted to us by authors worldwide. Together, we help to push the field of stem cell biology to new levels and toward safe and effective clinical application.

From the entire Editorial Board of STEM CELLS, we wish you a new year full of the best research and successful data and funding. We hope to see more success in translating stem cell, immunotherapy, and gene therapy advances into improved treatments for patients who need them. Happy New Year, and please continue to send us your best work in 2018!

REFERENCES

1 Uchida N, Haro-Mora JJ, Fujita A et al. Efficient generation of beta-globin-expressing erythroid cells using stromal cell-derived induced pluripotent stem cells from patients with sickle cell disease. STEM CELLS 2017;35:586–596.

2 Chen C, Termglinchan V, Karakikes I. Concise review: Mending a broken heart: The evolution of biological therapeutics. STEM CELLS 2017;35:1131–1140.

3 Adam S, Melguizo Sanchis D, El-Kamah G et al. Concise review: Getting to the core of inherited bone marrow failures. STEM CELLS 2017;35:284–298.

4 Okawa S, Gagrica S, Blin C et al. Proteome and secretome characterization of glioblastoma-derived neural stem cells. STEM CELLS 2017;35:967–980.

5 Orzan F, De Bacco F, Crisafulli G et al. Genetic evolution of glioblastoma stem-like cells from primary to recurrent tumor. STEM CELLS 2017;35:2218–2228.

6 Revenco T, Lapouge G, Moers V et al. Low dose radiation causes skin cancer in mice and has a differential effect on distinct epidermal stem cells. STEM CELLS 2017;35:1355–1364.

7 Mas A, Stone L, O'connor PM et al. Developmental exposure to endocrine disruptors expands murine myometrial stem cell compartment as a prerequisite to leiomyoma tumorigenesis. STEM CELLS 2017;35:666–678.

8 Yang T, Cheng J, Yang Y et al. S100B mediates stemness of ovarian cancer stem-like cells through inhibiting p53. STEM CELLS 2017;35:325–336.

9 Lee JH, Salci KR, Reid JC et al. Brief report: Human acute myeloid leukemia reprogramming to pluripotency is a rare event and selects for patient hematopoietic cells devoid of leukemic mutations. STEM CELLS 2017;35:2095–2102.

10 Kanehira M, Fujiwara T, Nakajima S et al. An lysophosphatidic acid receptors 1 and 3 axis governs cellular senescence of mesenchymal stromal cells and promotes growth and vascularization of multiple myeloma. STEM CELLS 2017;35:739–753.

11 Liotti F, Collina F, Pone E et al. Interleukin-8, but not the related chemokine CXCL1, sustains an autocrine circuit necessary for the properties and functions of thyroid cancer stem cells. STEM CELLS 2017;35:135–146.

12 Fierro FA, Nolta JA, Adamopoulos IE. Concise review: stem cells in osteoimmunology. STEM CELLS 2017;35:1461–1467.

13 Wang Y, Liu J, Jiang Q et al. Human adipose-derived mesenchymal stem cell-secreted CXCL1 and CXCL8 facilitate breast tumor growth by promoting angiogenesis. STEM CELLS 2017;35:2060–2070.

14 Christensen AG, Ehmsen S, Terp MG et al. Elucidation of altered pathways in tumor-initiating cells of triple-negative breast cancer: A useful cell model system for drug screening. STEM CELLS 2017;35:1898–1912.

15 Zuo WL, Yang J, Gomi K et al. EGF-amphiregulin interplay in airway stem/progenitor cells links the pathogenesis of smoking-induced lesions in the human airway epithelium. STEM CELLS 2017;35:824–837.

16 Oittinen M, Popp A, Kurppa K et al. Polycomb repressive complex 2 enacts Wnt signaling in intestinal homeostasis and contributes to the instigation of stemness in diseases entailing epithelial hyperplasia or neoplasia. STEM CELLS 2017;35:445–457.

17 Wu DC, Wang SSW, Liu CJ et al. Reprogramming antagonizes the oncogenicity of HOXA13-long noncoding RNA HOTTIP axis in gastric cancer cells. STEM CELLS 2017;35:2115–2128.

18 Mao J, Liang Z, Zhang B et al. UBR2 enriched in p53 deficient mouse bone marrow mesenchymal stem cell-exosome promoted gastric cancer progression via Wnt/beta-catenin pathway. STEM CELLS 2017;35:2267–2279.

19 Izumi D, Ishimoto T, Miyake K et al. Colorectal cancer stem cells acquire chemoresistance through the upregulation of F-Box/WD repeat-containing protein 7 and the consequent degradation of c-Myc. STEM CELLS 2017;35:2027–2036.

20 Vanova T, Konecna Z, Zbonakova Z et al. Tyrosine kinase expressed in hepatocellular carcinoma, TEC, controls pluripotency and early cell fate decisions of human pluripotent stem cells via regulation of fibroblast growth factor-2 secretion. STEM CELLS 2017;35:2050–2059.

21 Yao JC, Link DC. Concise review: The malignant hematopoietic stem cell niche. STEM CELLS 2017;35:3–8.

22 Lee AS, Tang C, Hong WX et al. Brief report: External beam radiation therapy for the treatment of human pluripotent stem cell-derived teratomas. STEM CELLS 2017;35:1994–2000.

23 Ahmed M, Chaudhari K, Babaei-Jadidi R et al. Concise review: Emerging drugs targeting epithelial cancer stem-like cells. STEM CELLS 2017;35:839–850.

24 Jain MD, Davila ML. Concise review: Emerging principles from the clinical application of chimeric antigen receptor T cell therapies for B cell malignancies. STEM CELLS 2017;

25 Relation T, Dominici M, Horwitz EM. Concise review: An (im)penetrable shield: How the tumor microenvironment protects cancer stem cells. STEM CELLS 2017;35:1123–1130.

26 Kobayashi M, Nabinger SC, Bai Y et al. Protein tyrosine phosphatase PRL2 mediates notch and kit signals in early T cell progenitors. STEM CELLS 2017;35:1053–1064.

27 Sontag S, Forster M, Qin J et al. Modelling IRF8 deficient human hematopoiesis and dendritic cell development with engineered iPS cells. STEM CELLS 2017;35:898–908.

28 He J, Rong Z, Fu X et al. A safety checkpoint to eliminate cancer risk of the immune evasive cells derived from human embryonic stem cells. STEM CELLS 2017;35:1154–1161.

29 Diaz MF, Vaidya AB, Evans SM et al. Biomechanical forces promote immune regulatory function of bone marrow mesenchymal stromal cells. STEM CELLS 2017;35:1259–1272.

30 Munir H, Ward LSC, Sheriff L et al. Adipogenic differentiation of mesenchymal stem cells alters their immunomodulatory properties in a tissue-specific manner. STEM CELLS 2017;35:1636–1646.

31 Li CL, Leng Y, Zhao B et al. Human iPSC-MSC-derived xenografts modulate immune responses by inhibiting the cleavage of caspases. STEM CELLS 2017;35:1719–1732.

32 Souidi N, Stolk M, Rudeck J et al. Stromal cells act as guardians for endothelial progenitors by reducing their immunogenicity after co-transplantation. STEM CELLS 2017;35:1233–1245.

33 Bowles AC, Wise RM, Gerstein BY et al. Immunomodulatory effects of adipose stromal vascular fraction cells promote alternative activation macrophages to repair tissue damage. Stem Cells 2017;35:2198–2207.
34 Amouzegar A, Mittal SK, Sahu A et al. Mesenchymal stem cells modulate differentiation of myeloid progenitor cells during inflammation. Stem Cells 2017;35:1532–1541.
35 Yang B, Hamilton JA, Valenzuela KS et al. Multipotent adult progenitor cells enhance recovery after stroke by modulating the immune response from the spleen. Stem Cells 2017;35:1290–1302.
36 Loisel S, Dulong J, Menard C et al. Brief report: Proteasomal indoleamine 2,3-dioxygenase degradation reduces the immunosuppressive potential of clinical grade-mesenchymal stromal cells undergoing replicative senescence. Stem Cells 2017;35:1431–1436.
37 Rashedi I, Gomez-Aristizabal A, Wang XH et al. TLR3 or TLR4 activation enhances mesenchymal stromal cell-mediated Treg induction via notch signaling. Stem Cells 2017; 35:265–275.
38 Davies LC, Heldring N, Kadri N et al. mesenchymal stromal cell secretion of programmed death-1 ligands regulates T cell mediated immunosuppression. Stem Cells 2017;35:766–776.
39 Lappin TR. A tale of two sisters. Stem Cells Translational Medicine 2013;2:481–482. doi: 10.5966/sctm.2013-0091

