BIOGRAPHICAL SKETCH

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NAME: Yong Zhao

eRA COMMONS USER NAME (credential, e.g., agency login): YZHAO21768

POSITION TITLE: Associate Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Weifang Medical College, Shandong China	M.D.	7/1990	Clinical Medicine
Shandong Academy of Medical Sciences, China	M.S.	7/1995	Immunology
Shanghai Second Military Medical University, China	Ph.D.	6/2000	Immunology
University of Chicago/Argonne National Lab, IL	Postdoc	8/2004	Cell Biology/Stem Cells

A. Personal Statement

My background in immunology, clinical trials, and stem cell biology provides a strong basis for designing, directing and performing the proposed studies. Specifically, by leading clinical trials in China and Spain over the past seven years, I have gained appreciable experience in clinical immunology and the regeneration of islet β cells in Type I Diabetes (T1D) subjects. Through my clinical training as a physician, I have had considerable experience working directly with T1D patients. Over the last 10 years, I have developed the Stem Cell Educator technology, starting with identification of a novel type of stem cells in cord blood CB-SCs and progressing to mechanistic studies in diabetic mice, preclinical studies , and, now, human clinical trials. The Stem Cell Educator therapy has recently been patented (*Note: Stem Cell Educator patent # US9,101,726 was granted by United States Patent and Trademark Office and other major countries such as Canada, EU, China, Japan, Korea, and Australia*). As Principal Investigator, I have led several international clinical trials to test the safety and therapeutic potential of Stem Cell Educator therapy for the treatment of T1D in adults (in China and Spain) (NCT01350219), T1D in children (NCT01996228), type 2 diabetes (NCT01415726), and alopecia areata (NCT01673789). Recently, four-year follow-up studies demonstrated the long-term safety and clinical efficacy of SCE therapy for the treatment of T1D and T2D. In 2013 and 2014, the Stem Cell Educator technology was the top third in rankings over 382 T1D clinical trials as released by the Juvenile Diabetes Cure Alliance and the State of Cure Report. My cumulative experience and expertise make me very well qualified to lead the proposed work and to accomplish the project goals through our established collaborations.

B. Positions and Honors:

Positions and Employment

1990 – 1992 Resident, Department of Internal Medicine, Qihe People's Hospital, Shandong, China
1995 – 1997 Attending Doctor, Shandong University, Qianfoshan Hospital, Shandong, China
2004 – 2012 Assistant Professor, Department of Medicine, University of Illinois, Chicago, IL, USA
2011 – CEO and President, Tianhe Stem Cell Biotechnologies Inc. IL, USA
2013 – Associate Scientist, Hackensack University Medical Center, Hackensack, NJ, USA
2013 – Visiting Professor, Shandong University, Jinan Central Hospital, Shandong, China
2014 – Visiting Professor, Hebei Medical University, Shijiazhuang, Hebei, China
2016 – Distinguished Professor, the 2nd Xiangya Hospital of Central South University, Changsha, Hunan, China

Professional Memberships

2003 –	American Diabetes Association
2002 –	The International Society for Stem Cell Research
2009 –	Immunology of Diabetes Society (IDS)
2002 – 2003	American Association for Cancer Research
2002 – 2003	American Association for the Advancement of Science
1995 – 2000	Chinese Society of Immunology

Honors

2013	BMC Medicine's Translational Medicine Award for Stem Cell Educator therapy in type 1 diabetes
2011	China Jinan 5150 Program Award for overseas scholar
2008	Rachmiel Levine Scientific Achievement Award (City of Hope, CA, USA)
2006	Rachmiel Levine Scientific Achievement Award (City of Hope, CA, USA)
1997	Advance of Medical Scientific Technology Prize, Shan Dong Province's Award for the Advance of Medical Technology
1996	Advance of Shan Dong Province's Scientific Technology (second prize) by the Shan Dong Province's Award of Scientific Technology

C. Contributions to Science:

1. Identification of Multipotent Stem Cells in Peripheral Blood and Human Cord Blood

My early work was dedicated to identifying pluripotent stem cells in peripheral blood and in human cord blood. I identified CB-SC as a novel type of stem cell by their particular adherence properties. These cells display a unique phenotype, with both embryonic and hematopoietic markers that distinguish them from other known stem cell types, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPC), and monocyte-derived stem cells. Phenotypic characterization demonstrates that CB-SCs display embryonic cell markers (e.g., transcription factors OCT-4 and Nanog, stage-specific embryonic antigen (SSEA)-3, and SSEA-4) and leukocyte common antigen CD45, but they are negative for blood cell lineage markers (e.g., CD1a, CD3, CD4, CD8, CD11b, CD11c, CD13, CD14, CD19, CD20, CD34, CD41a, CD41b, CD83, CD90, CD105, and CD133). They can give rise to three embryonic layer-derived cells in the presence of different inducers. More specifically, CB-SCs adhere tightly to culture dishes, with a large rounded morphology, and are resistant to common cell detachment methods (trypsin/EDTA), making it easy to collect suspended lymphocytes and isolate them from CB-SCs after ex-vivo co-culture. This was an important first step for the development of the Stem Cell Educator technology, as the technology is dependent upon the unique properties of cord blood stem cells, which have properties of both embryonic and hematopoietic stem cells.

a. **Yong Zhao**, Zhihua Huang, Meirigeng Qi, Ping Lazzarini, Theodore Mazzone. Immune regulation of T lymphocyte by a newly characterized human umbilical cord blood stem cell. *Immunology Letters.*108:78-87, 2007. PMID: 17161871.
b. **Yong Zhao**, Honglan Wang, Theodore Mazzone. Identification of stem cells from human umbilical cord blood with embryonic and hematopoietic characteristics. *Experimental Cell Research.* 312: 2454-2464, 2006. PMID: 16716296.
c. **Yong Zhao**, Theodore Mazzone. Human umbilical cord blood-derived f-macrophages retain pluripotentiality after thromboprotein expansion. *Experimental Cell Research.* 310: 311-318, 2005. PMID: 16143325.
d. **Yong Zhao**, David Glesne, Eliezer Huberman. A human peripheral blood monocyte-derived subset acts as pluripotent stem cells. *Proc. Natl Acad. Sci. USA.* 100: 2426, 2003. PMID: 12606720.

2. Development of Stem Cell Educator

I invented Stem Cell Educator devices and established the Stem Cell Educator therapy by using cord blood-derived multipotent stem cells (CB-SCs). This trial demonstrated that Stem Cell Educator therapy functions as "an artificial thymus" that circulates a patient's blood through a blood cell separator, briefly co-cultures the patient's lymphocytes with CB-SCs *in vitro*, induces immune tolerance through the action of autoimmune

regulator (AIRE), returns the educated **autologous** lymphocytes to the patient's circulation, and restores immune balance and homeostasis.

a. **Yong Zhao***. Stem Cell Educator Therapy and Induction of Immune Balance. Current Diabetes Reports. 12(5):517-23, 2012. PMID: 22833322
b. **Yong Zhao**, Theodore Mazzone. Human cord blood stem cells and the journey to a cure for type 1 diabetes. Autoimmunity Reviews. 10:103-107, 2010. PMID: 20728583
c. International Patent: PCT/US2010/059522, Inventor: **Yong Zhao**, Title: STEM CELL IMMUNE MODULATION METHODS OF USE AND APPARATUS. This PCT patent has been granted by the United States Patent and Trademark Office (USPTO) with application #13/514, 694, patent #US9,101,726.
d. US Patent: US 9388382, Inventor: **Yong Zhao**, Theodore Mazzone, Title: Isolation of CD14 negative, CD45 positive and CD117 positive embryonic-like stem cells free of monocytes from human umbilical cord blood mononuclear cells. This PCT patent has been granted by the United States Patent and Trademark Office (USPTO).

3. Application of Human Cord Blood Stem Cells in Early Phase Clinical Trials

I have served as PI of several Phase I/II clinical trials to test the Stem Cell Educator technology in patients with Type 1 Diabetes, Type 2 Diabetes, and autoimmune-caused Alopecia Areata (AA). In all cases, the patients saw a reversal of the disease symptoms. Notably, our T1D clinical trial reveals that a single treatment with the Stem Cell Educator provides lasting reversal of autoimmunity that allows regeneration of islet β cells and improvement of metabolic control in individuals with longstanding T1D. Due to limitations in obtaining human pancreatic islets following Stem Cell Educator therapy, we used this AA trial to examine the molecular effects of therapy on the affected tissue. Findings from the Alopecia Areata trial provide visible evidence that Stem Cell Educator therapy can control autoimmunity and lead to the regeneration of tissues like hair regrowth. Here, we found that the expression of TGF-β1 encircled human hair follicles, similar to the "ring of TGF-β1" we previously found around pancreatic islets in treated diabetic NOD mice. It provides a novel molecular mechanism underlying the immune modulation of Stem Cell Educator therapy.

a. Delgado E, Perez-Basterrechea M, Suarez-Alvarez B, Zhou H, Martinez Revuelta E, Garcia-Gala JM, Perez S, Avrez-Viejo M, Menendez E, Lopez-Larrea C, Tang R, Zhu Z, Hu W, Moss T, Guindi E, Otero J, and **Zhao Y**. Modulation of autoimmune T-Cell memory by Stem Cell Educator therapy: phase 1/2 clinical trial. EBioMedicine 2015, 2, 2024-2036. PMID: 26844283.
b. Yanjia Li, Baoyong Yan, Hepeng Wang, Heng Li, Quanhai Li, Dong Zhao, Yana Chen, Ye Zhang, Wenxia Li, Jun Zhang, Shanfeng Wang, Jie Shen, Yunxiang Li, Edward Guindi, **Yong Zhao**. Hair regrowth in alopecia areata patients following Stem Cell Educator therapy. *BMC Medicine*. 13: 87, 2015. PMID: 25896390.
c. **Yong Zhao,** Zhaoshun Jiang, Tingbao Zhao, Mingliang Ye, Chengjin Hu, Huimin Zhou, Zhaohui Yin, Yana Chen, Ye Zhang, Shanfeng Wang, Jie Shen, Hatim Thaker, Summit Jain, Yunxiang Li, Yalin Diao, Yingjian Chen, Xiaoming Sun, Mary Beth Fisk, Heng Li. Targeting insulin resistance in type 2 diabetes via immune modulation of cord blood-derived multipotent stem cells (CB-SCs) in stem cell educator therapy: phase I/II clinical trial. *BMC Medicine.* 11: 160, 2013. PMID: 23837842.
d. **Yong Zhao**, Zhaoshun Jiang, Tingbao Zhao, Mingliang Ye, Chengjin Hu, Zhaohui Yin, Heng Li, Ye Zhang, Yalin Diao, Yunxiang Li, Yingjian Chen, Xiaoming Sun, Mary Beth Fisk, Randal A. Skidgel, Mark Holterman, Bellur Prabhakar, Theodore Mazzone. Reversal of Type 1 Diabetes via Islet beta Cell Regeneration Following Immune Modulation by Cord Blood-Derived Multipotent Stem Cells. *BMC Medicine.* 10(1): 3, 2012. PMID: 22233865.

4. Mechanistic Studies of the Stem Cell Educator Therapy in Humans

Based on our combined preclinical and clinical studies to date, immune modulation by CB-SCs seems to be mediated by a variety of molecular and cellular mechanisms as follows: 1) expression of autoimmune regulator (AIRE) in CB-SCs plays an essential role; 2) functioning via cell-cell contact mechanisms involving the surface molecule programmed death ligand 1 (PD-L1) and CD270 on CB-SCs, and their ligands PD-1 and BTLA on a variety of immune cells (e.g., T cells, B cells, monocytes, dendritic cells, and granulocytes); 3) acting through soluble factors released by CB-SCs (e.g., nitric oxide, TGF-β1); and 4) adjusting the cell-cell interaction between antigen-presenting cells such as monocytes/macrophages and T cells through costimulating

molecules and their ligands. Thus, during the *ex vivo* brief exposure to CB-SCs, T1D-derived T_{CM} and T_{EM} can be "educated" by the favorable microenvironment created by CB-SCs through cell-to-cell contact and soluble factors. Additionally, my previous work demonstrated that CB-SCs have significant effects on the suppression and elimination of islet antigen-specific pathogenic T cells. Recently, we found that platelet counts were increased in diabetic subjects after receiving SCE therapy. Platelets display immune tolerance-associated markers (e.g., autoimmune regulator and programmed death ligand-1) and pancreatic islet β-cell-associated markers that are encoded by platelet mitochondrial DNA. Immunohistochemical studies of pancreatic islets revealed a critical difference between Caucasian and Chinese islet β cells that may underlie the difference in response. Specifically, muscarinic acetylcholine receptor M2 (one of the G_i/G_o-protein–coupled receptors) and certain cholinergic markers such as vesicular acetylcholine transporter (vAChT) or choline acetyltransferase (ChAT) are strongly expressed on the islet β cells of the Chinese population but only very weakly or not expressed on the islet β cells of the Caucasian population. Interestingly, these markers were found on the islet α cells of the Caucasian population.

a. **Yong Zhao**, Theodore Mazzone. Human cord blood stem cells and the journey to a cure for type 1 diabetes. Autoimmunity Reviews. 10:103-107, 2010. PMID: 20728583.
b. Delgado E, Perez-Basterrechea M, Suarez-Alvarez B, Zhou H, Martinez Revuelta E, Garcia-Gala JM, Perez S, Avrez-Viejo M, Menendez E, Lopez-Larrea C, Tang R, Zhu Z, Hu W, Moss T, Guindi E, Otero J, and **Zhao Y**. Modulation of autoimmune T-Cell memory by Stem Cell Educator therapy: phase 1/2 clinical trial. EBioMedicine 2015, 2, 2024-2036. PMID: 26844283.
c. Yanjia Li, Baoyong Yan, Hepeng Wang, Heng Li, Quanhai Li, Dong Zhao, Yana Chen, Ye Zhang, Wenxia Li, Jun Zhang, Shanfeng Wang, Jie Shen, Yunxiang Li, Edward Guindi, **Yong Zhao**. Hair regrowth in alopecia areata patients following Stem Cell Educator therapy. *BMC Medicine*. 13: 87, 2015. PMID: 25896390.
d. **Yong Zhao**, Brian Lin, Robert Darflinger, Yongkang Zhang, Mark J. Holterman, Randal A. Skidgel. Human cord blood stem cell-modulated regulatory T lymphocytes reverse the autoimmune-caused type 1 diabetes in nonobese diabetic (NOD) mice. *PLoS ONE* 2009;4:e4226. PMID: 19156219.

5. Platelet-Derived Mitochondria (pMitochondria) Represent a New Paradigm for Immune Therapy and Regenerative Medicine.

Conventionally, platelets are known mainly for their crucial role in thrombosis and hemostasis, and mitochondria as powerhouses of aerobic metabolism that produce 90% of cellular energy. But I have shown that expression of immune tolerance-, embryonic stem cell-, and islet β cell-associated factors in pMitochondria challenge these conventional notions of platelet and mitochondrial roles. *Ex vivo* studies indicate that human islet β cells are reprogrammed to proliferate while maintaining cell viability and restore β-cell function after taking up pMitochondria, thus demonstrating a novel and potentially transformative role for pMitochondria as a therapeutic modality. The concept of using pMitochondria as a novel therapeutic agent has the potential to revolutionize the stem cell-based regenerative medicine and other cell therapeutic approaches.

a. **Yong Zhao**, Zhaoshun Jiang, Elias Delgado, Heng Li, Huimin Zhou, Wei Hu, Marcos Perez-Basterrechea, Anna Janostakova, Qidong Tan, Jing Wang, Mao Mao, Zhaohui Yin, Ye Zhang, Ying Li, Quanhai Li, Jing Zhou, Yunxiang Li, Eva Martinez Revuelta, Jose Maria García-Gala, Honglan Wang, Silvia Perez-Lopez, Maria Alvarez-Viejo, Edelmiro Menendez, Thomas Moss, Edward Guindi, Jesus Otero. Platelet-derived mitochondria display embryonic stem cell markers and improve pancreatic islet β-cell function in humans. *Stem Cells Translational Medicine. Accepted for publication*. 2017.
b. US provisional patent application (#6457402). Inventor: **Yong Zhao**. Title: compositions and methods for reprogramming adult cells through the stemness of a platelet rich fraction of blood containing platelet-like cells in humans.

Complete List of Published Work on Stem Cell Educator technology (25 of 40 total papers authored)
http://www.ncbi.nlm.nih.gov/pubmed/?term=Zhao%2C+Yong%2C+stem+cell%2C+blood

D. Research Support

Ongoing Research Support

S2016G9086: Zhao Y (PI) and Zhou ZG (Co-PI in China) 10/1/2016 – 12/31/2019
Ministry of Science and Technology of the P.R. China. Cooperation projects in science and technology Between China and the US government
Stem Cell Educator therapy in type 1 diabetes: Clinical Translation and Molecular Mechanisms.

31528009 Zhao Y (PI) 01/01/2016 – 12/31/2018
National Natural Science Foundation of China, International Collaboration Program
Molecular mechanisms underlying Stem Cell Educator therapy for the treatment of diabetes

Zhao Y (PI) 07/15/2013 – 07/14/2019
Hackensack University Medical Center Foundation
Clinical Trials of Stem Cell Educator Therapy in Type 1 Diabetes and Alopecia Areata

81373635 Li XH (PI), Zhao Y (Co-PI) 01/01/2014 – 12/31/2017
National Natural Science Foundation of China
Therapeutic Potential of Cord Blood Stem Cells and Icariin in Alzheimer's disease

Completed Research Support in Last 3 Years

2011033 Zhao Y (PI) 07/12/2011 – 12/31/2016
Jinan 5150 Program for Oversea Scholar (China)
Human Cord Blood Stem Cells and Clinical Applications

201212012 Li XH (PI), Zhao Y (Co-PI) 11/12/2012 – 12/31/2015
Jinan Science & Technology Bureau (China)
Anti-Inflammatory Effects of Cord Blood Stem Cells and Therapeutic Potential in Alzheimer's disease

201101104 Li XH (PI), Zhao Y (Co-PI) 04/07/2011 – 12/31/2014
Jinan Science & Technology Bureau (China)
Differentiation of Adult Peripheral Blood-Derived Stem Cells into Dopamine-Neurons and Their Therapeutic Potential in Parkinson's disease

17-2012-541 Atkinson M (PI), Zhao Y (Co-PI) 09/01/2012 – 02/28/2014
Juvenile Diabetes Research Foundation International (JDRF)
Ex Vivo Analysis of the Cell Educator System