2020年国际干细胞论坛

The 2020 International Forum on Stem Cells Virtual

2020年11月18-19日
November 18-19, 2020

会议手册 Program Book

主 办 单 位：中国医学科学院血液病医院（中国医学科学院血液学研究所）
实验血液学国家重点实验室
国家血液系统疾病临床医学研究中心
中国细胞生物学学会干细胞生物学分会

Organized by: Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences
State Key Laboratory of Experimental Hematology
National Clinical Research Centre for Blood Diseases
Chinese Society for Stem Cell Biology, Chinese Society for Cell Biology

协 办 单 位：中国医学科学院北京协和医学院
中国生理学会血液学专业委员会
中国-以色列人群医学“一带一路”联合实验室
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Program of 2020 International Forum on Stem Cells Virtual Meeting

November 18-19, 2020

11/18/2020, Wednesday	
8:00-8:10	**Welcome Ceremony and Opening Remarks**
8:10-9:00 **I Keynote speech I** **Chair:** Tao Cheng	1. Title: Remembrance of things past: turning on fetal hemoglobin to treat hemoglobin disorders for therapy Speaker: Stuart Orkin Harvard University, USA
9:00-10:15 **II Stem cell gene therapy** (Each talk 25 mins, including 5 mins discussion) **Chairs:** Lee Grimes Linheng Li	2. Title: Programming and reprograming of aging Speaker: Guanghui Liu Chinese Academy of Sciences, China
	3. Title: BCL11A enhancer editing for the beta-hemoglobin disorders Speaker: Yuxuan Wu East China Normal University, China
	4. Title: Transform cell and organ therapy using genome editing Speaker: Luhan Yang Hangzhou Qihan Biotech, China
10:25-11:40 **III Stem cell diseases and target therapy** (Each talk 25 mins, including 5 mins discussion) **Chairs:** Nadia Carlesso Min Wang	5. Title: Bcl-xl PROTAC–A safer and more effective therapeutic agent for hematologic malignancies Speaker: Daohong Zhou University of Florida, USA
	6. Title: Hematopoietic stem cell heterogeneity is associated with myeloproliferative neoplasm Speaker: Lihong Shi Chinese Academy of Medical Sciences, China
	7. Title: Anti-IL-2 preserves graft versus leukemia activity while preventing graft versus host disease Speaker: Defu Zeng City of Hope, USA
11:40-15:00	**Lunch Break**

15:00-16:40 **IV Hematopoietic stem and progenitor cells** (Each talk 25 mins, including 5 mins discussion) **Chairs:** Simón Méndez-Ferrer Bing Liu	8. Title: Notch ligands orchestrate the generation of hematopoietic stem Scells in the embryo Speaker: Anna Bigas Institut Hospital del Mar d'Investigacions Mèdiques, Spain
	9. Title: Engraftment of functional human hematopoietic stem cells in mice Speaker: Claudia Waskow Leibniz Institute on Aging, Germany
	10. Title: Multi-scale analysis of haematopoietic stem/progenitor cell function Speaker: Bertie Göttgens University of Cambridge, UK
	11. Title: Human haematopoietic stem and progenitor cell landscapes: location matters Speaker: Elisa Laurenti University of Cambridge, UK
16:50-18:30 **V Tissue regenerative and repair** (Each talk 25 mins, including 5 mins discussion) **Chair:** Terry Lappin Ding Ai	12. Title: Decoding the heterogenous vascular niche in lung regeneration Speaker: Bisen Ding Sichuan University, China
	13. Title: Developing cell therapies for vascular repair in diabetes Speaker: Reinhold Medina Queen's University Belfast, UK
	14. Title: Revealing cellular heterogeneity, developmental trajectory and novel subpopulations with immune functions in megakaryocytes Speaker: Jiaxi Zhou Chinese Academy of Medical Sciences, China
	15. Title: Mitochondrial transfer by mesenchymal stem cells as a strategy for lung repair Speaker: Anna Krasnodembskaya Queen's University Belfast, UK

11/19/2020, Thursday

8:00-8:50 **VI Keynote speech II** **Chair:** Linzhao Cheng	16. Title: Regenerative medicine: current concepts and changing trends Speaker: Anthony Atala Wake Forest School of Medicine, USA
8:50-10:05 **VII Regenerative medicine** (Each talk 25 mins, including 5 mins discussion) **Chairs:** Hideo Ema Jinyong Wang	17. Title: Hematopoietic stem cell expansion: developmental pathway and clinical results Speaker: John Wagner University of Minnesota, USA
	18. Title: Use of human pluripotent stem cells to identify novel regulators of immune cell activity Speaker: Dan Kaufman University of California at San Diego, USA
	19. Title: CAR-NK cells from engineered pluripotent stem cells: off-the-shelf therapeutics for all patients Speaker: Shijiang Lu HebeCell Corporation, USA
10:15-11:30 **VIII Molecular mechanism and network** (Each talk 25 mins, including 5 mins discussion) **Chairs:** Jiwang Zhang Jia Yu	20. Title: RNA-binding proteins harness RNA and phase separation to modulate transcription in pluripotent stem cells Speaker: Xiaohua Shen Tsinghua University, China
	21. Title: Deciphering new mechanisms of HSC fate determination in vertebrates Speaker: Feng Liu Chinese Academy of Sciences, China
	22. Title: Single-cell transcriptomes of blood cells and beyond Speaker: Ping Zhu Chinese Academy of Medical Sciences, China
11:30-15:00	**Lunch Break**

15:00-17:05 **IX CAMS-PUMC Webinar Series -- Belt and Road Leaders** (Each talk 25 mins, including 5 mins discussion) **Chairs:** Tsvee Lapidot Hui Cheng Lai Guan NG	23. Title: An instructive role for IL7RA in the development of human B-cells and B cell precursor leukemia Speaker: Shai Izraeli Tel Aviv University, Israel
	24. Title: Gene editing and high-throughput functional genomics Speaker: Wensheng Wei Peking University, China
	25. Title: The aging of the blood system Speaker: Liran Shlush The Weizmann Institute of Science, Israel
	26. Title: Identify Pancreatic Islet Resident Progenitors Speaker: Yi Zeng Chinese Academy of Sciences, China
	27. Title: Epithelial cell therapies for kidney disease Speaker: Benjamin Dekel Tel Aviv University, Israel
17:05-17:15	**Closing Remarks**

Tao Cheng

Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, China

Biography

Tao Cheng is currently a professor of medicine at Peking Union Medical College (PUMC) and Chinese Academy of Medical Sciences (CAMS), president of Institute of Hematology & Blood Diseases Hospital at CAMS, director of State Key Laboratory of Experimental Hematology, and also the founding chairman of Department of Stem Cell and Regenerative Medicine at PUMC, the founding director of Center for Stem Cell Medicine at CAMS and the founding president of Chinese Association for Blood Sciences (CABS).

Prof. Cheng received his medical degrees from Second Military Medical University in Shanghai, China (1981-1989). He did his residency in internal Medicine and clinical fellowship in Hematology at Changhai Hospital, Shanghai, China (1989-1993). He received his postgraduate research training at Hipple Cancer Research Center, Dayton, Ohio and Massachusetts General Hospital, Boston, Massachusetts (1993-1997). He became an instructor in Medicine in 1998, then an assistant professor in 2001 at Harvard University, an associate professor with tenure (2006-2010) and later a full professor at University of Pittsburgh School of Medicine (2010-2013).

Prof. Cheng‘s laboratory primarily focuses on both genetic and epigenetic mechanisms in hematopoietic stem and progenitor cells, with each project guided by approaches intended to elucidate basic principles and develop practical strategies. Leukemia and bone marrow failure are the main diseases against which research advances in the laboratory are achieved. Through broadly collaborative approaches, Prof. Cheng is also committed to training hematologists and stem cell biologists, and to building strong hematology and stem cell research programs that will ultimately benefit the patients.

Prof. Cheng is the founding editor-in chief of Blood Science, the first English fundamental hematology journal in China. He has been in the editorial board of several leading journals in hematology and stem cell research including Blood, Leukemia, Experimental Hematology (associate editor) and International Journal of Hematology (associate editor).

Bertie Göttgens

University of Cambridge, UK

Biography

Bertie Göttgens graduated from Tübingen University in 1992 with a degree in biochemistry and received his DPhil in biological sciences from the University of Oxford in 1994. He then moved to the University of Cambridge Department of Haematology for postdoc training from 1994 to 2003 before becoming a Leukaemia Research Fund Lecturer and then a University Lecturer (2003-2007). He was appointed Reader in Molecular Haematology in 2007 and since 2011 has been the University of Cambridge Professor of Molecular Haematology. In 2019 he was appointed Deputy Director of the Wellcome – MRC Cambridge Stem Cell Institute. Amongst other appointments he is an Associate Editor of Blood and a former president of the International Society of Experimental Hematology. He is a fellow of the Academy of Medical Sciences and a member of EMBO.

Bertie uses a combination of experimental and computational approaches to study how transcription factor networks control the function of blood stem cells and how mutations that perturb such networks cause leukaemia. This integrated approach has resulted in the discovery of new combinatorial interactions between key blood stem cell regulators, as well as experimentally validated computational models for blood stem cells. Current research focuses on (i) single cell genomics of early blood development, (ii) modelling the transcriptional landscape of blood stem and progenitor cell differentiation, (iii) transcriptional consequences of leukaemogenic mutations in leukaemia stem/progenitor cells, and (iv) molecular characterisation of human blood stem/progenitor cell populations used in cell and gene therapy protocols.

Abstract

Multi-scale Analysis of Haematopoietic Stem/Progenitor Cell Function

Homeostasis of the haematopoietic system is achieved through carefully balanced proliferation, differentiation and cell death, to maintain appropriate numbers of all the various haematopoietic cell types. Malignant as well as non-malignant diseases impact the very same cellular processes, thus disrupting the overall balance between cell types. Historically, it has been difficult to connect “molecular scale” processes, such as leukaemogenic mutations, with their likely “tissue scale” consequences, such as the resulting dynamic alterations of the entire haematopoietic system. The principal reason behind this disconnect is that tissue-scale analysis in the haematopoietic system is traditionally performed by FACS, which is limited because (i) only a small number of parameters can be assessed, and (ii) many FACS markers are not reliable indicators of cellular states following perturbation.

The advent of high throughput single cell molecular profiling promises to transform our ability to interpret perturbations of the haematopoietic system, because molecular level information can now be obtained for tens of thousands of cells, thus connecting the molecular with the whole tissue scales. This presentation will provide an update of the Göttgens group’s efforts on enhancing our understanding of haematopoiesis based on representations of the haematopoietic differentiation landscape generated from single cell expression profiles. High-throughput CrispR gene knock-out experiments are complemented with tissue modelling to identify comprehensive information on gene regulatory interactions in haematopoietic progenitor cells, as well as infer parameters that underpin normal homeostasis and allow the simulation of leukaemogenic mutations and possible treatments.

Stuart Orkin

Harvard University, USA

Biography

Dr. Stuart H Orkin is the David G. Nathan Distinguished Professor of Pediatrics at Harvard Medical School, and an HHMI Investigator at Boston Children's Hospital. Orkin has defined the molecular basis of human blood disorders and mechanisms governing blood cell development. Previously he served as Chairman of the Department of Pediatric Oncology at the Dana Farber Cancer Institute from 2000-2016. He received a BS from MIT and an MD from Harvard Medical School. Dr. Orkin served on the National Research Council Committee on Mapping the Human Genome and as co-chair of the Panel to Assess the NIH Investment in Gene Therapy. He was the inaugural chair of the Grants Reviews Committee of the California Institute of Regenerative Medicine (CIRM).

He provided the first comprehensive molecular dissection of an inherited disorder (the thalassemia syndromes), and characterized genes responsible for other human blood disorders, including X-linked chronic granulomatous disease (the first positional cloning). Orkin identified the first hematopoietic transcription factors (the GATA family) and characterized their roles in blood cell development and cancer. His studies of BCL11A, a repressor of fetal hemoglobin (HbF), have illuminated regulation of globin gene switching and improved prospects for HbF reactivation as therapy of the thalassemias and sickle cell disease.

Dr. Orkin was elected to the National Academy of Sciences (NAS), National Academy of Medicine (NAM), American Academy of Arts and Sciences, and the American Philosophical Society, He received the E. Mead Johnson Award, Warren Alpert Prize, Helmut Horten Foundation Prize, Distinguished Research Award from the Association of American Medical Colleges (AAMC), E. Donnall Thomas, Dameshek and Basic Science Mentor Awards of the American Society of Hematology (ASH). He received Jessie Stevenson Kovalenko Medal of the NAS for "important contributions to the medical sciences"(2013), the William A. Allan Award of the American Society of Human Genetics (2014), the George M. Kober Medal of the American Association of Physicians (2018), the Mechthild Esser Nemmers Prize in Medical Science of Northwestern University (2018), the King Faisal Prize in Medicine (2020), and the Harrington Prize for Innovation in Medicine (2020).

Abstract

Remembrance of things past: turning on fetal hemoglobin to treat hemoglobin disorders for therapy

In this presentation I will review what has been learned regarding the mechanism by which the critical switch from fetal (HbF) to adult-type (HbA) hemoglobin is regulated in the erythroid cell lineage during development. The major hemoglobin disorders, beta-thalassemia and sickle cell disease (SCD), are due to mutations in the beta-globin gene (the beta-like chain in HbA). Therefore, it was hypothesized decades ago that reactivation of HbF in adult erythroid cells would lessen the severity of the hemoglobin disorders. A formidable obstacle to this strategy was the lack of knowledge regarding how HbF is silenced in the fetal to adult transition. Beginning with GWAS in 2007/8, our group focused attention on BCL11A, a zinc-finger protein encoded on the short arm of chromosome 2. In a series of studies, we demonstrated that BCL11A is a major repressor of gamma-globin gene expression and its knockout in erythroid cells leads to robust reactivation of gamma-globin transcription and hence HbF production. Such reactivation is sufficient to rescue the SCD disease phenotype in engineered mice. Further, we showed that common genetic variation detected in GWAS resides in an erythroid-specific enhancer within the BCL11A gene and the enhancer is essential for BCL11A expression in the lineage. Through comprehensive CRISPR/Cas9 mutagenesis, we identified a discrete region of the enhancer encompassing a critical GATA-site that is required for a major portion of its activity. This region has become the target of current gene editing trials using both zinc-finger nucleases and CRISPR/Cas9. Detailed chromatin binding studies employing CUT&RUN and gene editing revealed that BCL11A acts directly within the gamma-globin promoter to repress expression and does so through displacement of a ubiquitous activator, NF-Y. To achieve maximum repression, BCL11A recruits the NuRD corepression complex to the promoter and acts in concert with a second repressor, LCR, that binds further upstream in the gamma-globin gene promoter. The detailed mechanistic understanding of HbF silencing has provided the foundation for ongoing clinical trials directed at BCL11A, using erythroid-specific shRNA, gene editing of the BCL11A enhancer, and destruction of the BCL11A binding site in the gamma-globin promoter. Preliminary results of clinical trials validate the preclinical science and have shown very promising benefit in SCD and beta-thalassemia. Taken together, the work illustrates how fundamental insights into developmental control can now be translated for definitive therapy of patients with life-threatening disease.

Anthony Atala

Wake Forest School of Medicine, USA

Biography

Anthony Atala, MD, is the G. Link Professor and Director of the Wake Forest Institute for Regenerative Medicine. His work focuses on growing human cells, tissues and organs. Dr. Atala works with several journals and serves in various roles, including Editor-in-Chief of: Stem Cells- Translational Medicine; and BioPrinting. Fifteen applications of technologies developed in Dr. Atala's laboratory have been used clinically. He is the editor of 22 books, has published more than 800 journal articles and has applied for or received over 250 national and international patents.

Dr. Atala was elected to the National Academy of Medicine, and is a recipient of the US Congress funded Christopher Columbus Foundation Award, bestowed on a living American who is currently working on a discovery that will significantly affect society; the Edison Science/Medical Award; the R&D Innovator of the Year Award; and the Smithsonian Ingenuity Award. Dr. Atala's work was listed twice as Time Magazine's top 10 medical breakthroughs of the year, and was ranked by the Project Management Institute as one of the top 10 most impactful biotech projects from the past 50 years. Dr. Atala was named by Scientific American as one of the world's most influential people in biotechnology, by U.S. News & World Report as one of 14 Pioneers of Medical Progress in the 21st Century, by Life Sciences Intellectual Property Review as one of 50 key influencers in the life sciences intellectual property arena, and by Nature Biotechnology as one of the top 10 translational researchers in the world.

Abstract

Regenerative Medicine: Current Concepts and Changing Trends

Patients with diseased or injured organs may be treated with transplanted tissues. There is a severe shortage of donor organs and tissues which is worsening yearly due to the aging population. Regenerative medicine and tissue engineering apply the principles of cell transplantation, material sciences, and bioengineering to construct biological substitutes that may restore and maintain normal function in diseased and injured tissues. Stem cells may offer a potentially limitless source of cells, and 3D bioprinting applications are being utilized for potential therapies. Recent advances that have occurred in regenerative medicine will be reviewed. Applications of these new technologies that offer novel therapies for patients with tissue injury and organ failure will be described.

Guanghui Liu

Institute of Zoology, Chinese Academy of Sciences, China

Biography

Guang-Hui Liu is a professor at the Institute of Zoology, Chinese Academy of Sciences. He aims to identify the mechanisms underlying human stem cell aging and their implications in human age-associated disorders. The mission of Dr. Liu's laboratory is to establish a global view on the factors contributing to or antagonizing human stem cell aging, and to develop novel therapeutic interventions for the goal of "healthy aging". Dr. Liu has published over 100 publications in Nature, Science, Cell, etc. prestigious journals. Dr. Liu has been an active member of the international scientific community; he is the president of Chinese Society of Aging Cell Research (CSACR), the Deputy Editor-in-Chief of Protein & Cell, an Associate Editor of Stem Cell Research & Therapy，and an editorial board member of Cell Reports and Aging Cell.

Abstract

Programming and reprograming of aging

Age is the major risk factor for most chronic human diseases. As a consequence, “geroprotective” strategies are being pursued as a way to prevent and treat age-related disorders.

As we age, our stem cells undergo functional decay and exhaustion. This decline leads to compromised tissue regeneration, which in turn promotes organismal aging. Therapeutic approaches that promote tissue regeneration and repair could therefore potentially mitigate aging and its deleterious effects.

Currently, there are three main methods to promote tissue regeneration: (1) Supplement tissues with exogenous stem/progenitor cells; (2) Chemically stimulate in-situ stem cell expansion, differentiation, and/or somatic cell transdifferentiation; and (3) Rejuvenate endogenous stem cell pools with specific biological factors. In animal models, these methods can alleviate diverse aging syndromes, including neurodegeneration, vascular degeneration, myocardial infarction and osteoarthritis. Technological advances allow us to further improve these strategies to repair degenerating organs. For instance, genetically enhanced stem cells and vascular cells with improved efficacy and safety were recently generated by editing longevity genes and tumor suppressors. Approaches to activate tissue regeneration could also be optimized by targeting cellular senescence and regeneration pathways. Overall, engineering tissues and organs that resist aging would transform regenerative medicine, providing a potential “silver bullet” against chronic disease.

Yuxuan Wu

East China Normal University, China

Biography

Dr. Yuxuan Wu trained in the laboratories of Jinsong Li in Chinese Academy of Sciences and Daniel Bauer in Harvard Medical School, where he studied pluripotency of embryonic stem cells, CRISPR mediated genome editing in hematopoietic stem cells. His research program focuses on understanding the molecular mechanisms that regulate self-renewal and differentiation of hematopoietic stem cells, as well as the CRISPR mediated highly efficient gene editing in human hematopoietic stem cells for the beta-thalassemia and sickle cell disease.

Abstract

BCL11A enhancer editing for the beta-hemoglobin disorders

Re-expression of the paralogous gama-globin genes (HBG1/2) could be a universal strategy to ameliorate the severe β-globin disorders sickle cell disease (SCD) and beta-thalassemia by induction of fetal hemoglobin. Previously we and others have shown that core sequences at the BCL11A erythroid enhancer are required for repression of HbF in adult-stage erythroid cells but dispensable in non-erythroid cells. CRISPR-Cas9 mediated gene modification has demonstrated variable efficiency, specificity, and persistence in hematopoietic stem cells (HSCs). Here we demonstrate that Cas9:sgRNA ribonucleoprotein (RNP) mediated cleavage within a GATA1 binding site at the +58 BCL11A erythroid enhancer results in highly penetrant disruption of this motif, reduction of BCL11A expression, and induction of HbF. We optimize conditions for selection-free on-target editing in patient-derived HSCs as a nearly complete reaction lacking detectable genotoxicity or deleterious impact on stem cell function. HSCs preferentially undergo nonhomologous as compared to microhomology mediated end-joining repair. Erythroid progeny of edited engrafting sickle cell disease (SCD) HSCs express therapeutic levels of fetal hemoglobin (HbF) and resist sickling, while those from beta-thalassemia patients show restored globin chain balance. NHEJ-based BCL11A enhancer editing approaching complete allelic disruption in HSCs is a practicable therapeutic strategy to produce durable HbF induction.

Luhan Yang

Hangzhou Qihan Biotech, China

Biography

Dr. Luhan Yang is Chief Executive Officer of Qihanbio, a company revolutionizing the field of transplantation with an unparalleled, multiplexed gene editing platform for the development of human-compatible organs, tissues and cells. Dr. Yang leads a world class genome engineering team harnessing the latest gene-editing techniques with the capability to solve the global organ crisis by reinvigorating the field of xenotransplantation and offering the potential to expand the applicability of transplantation into other areas such as cell therapy. She previously developed the highly programmable genome-engineering tool, CRISPR/Cas9, for use in mammalian cells, and pioneered the first isogenic human stem cell lines to model human diseases at the tissue level. She was recently honored in the Bloomberg 50 (2017), named “Young Global Leader” by the World Economic Forum (2017) and was featured in “30 Under 30” in Science and Healthcare by Forbes Magazine (2014).

Abstract

Transform cell and organ therapy using genome editing

Cell therapy is quickly becoming an indispensable weapon against cancer and other serious diseases, yet the technology behind cell therapy leaves much room for improvement. Autologous, or personalized, cell therapies can be prohibitively expensive, while allogeneic approaches to cell therapy still require the patient to be administered immunosuppressive drugs and have been prone to rejection by the immune system.

Qihan aims to use high-throughput, multiplexable genome editing in combination with expertise in transplantation immunology to create immunologically privileged allogeneic cells and xenogeneic organs for use as therapies to treat cancer, organ failure and other important medical conditions.

Daohong Zhou

University of Florida, USA

Biography

Dr. Daohong Zhou is a Professor in the Department of Pharmacodynamics at the College of Pharmacy and a Professor in the Department of Radiation Oncology at the College of Medicine, University of Florida (UF) at Gainesville. He serves as the Associate Director for Translation and Drug Development and the Harry E. Innes Endowed Professor of Cancer Research at the UF Health Cancer Center. His research has led to a better understanding of the role of cellular senescence in ionizing radiation (IR) and chemotherapy induced normal tissue damage (such as bone marrow suppression and pulmonary fibrosis) and the discovery of the first potent and broad-spectrum senolytic agent, ABT263 (a dual Bcl-2 and Bcl-xl inhibitor), that can selectively kill senescent cells to rejuvenate both prematurely senescent tissue stem cells (including hematopoietic stem cells) induced by IR and tissue stem cells in normally aged mice. This discovery may lead to new therapeutics for various age-related diseases and the side effects induced by chemotherapy and IR. More recently, he developed several proteolysis targeting chimeras (PROTACs) that can target Bcl-xl and other proteins of interest for degradation via the ubiquitination and proteasome system. He found that Bcl-xl PROTACs can selectively induce Bcl-xl degradation in senescent cells and various cancer cells but not in platelets, suggesting that Bcl-xl PROTACs have the potential to be developed as a better senolytic and anticancer agent than ABT263 by not causing thrombocytopenia. Using the PROTAC drug development platform, he is developing additional specific antitumor and better senolytic agents.

Abstract

Bcl-xl PROTAC–A safer and more effective therapeutic agent for hematologic malignancies

B-cell lymphoma extra large (BCL-X_L) is a well-validated tumor target. However, the on-target and dose-limiting thrombocytopenia limits the use of BCL-X_L inhibitors, such as ABT263, as safe and effective antitumor agents. To reduce the toxicity of ABT263, we converted it into DT2216, a BCL-X_L proteolysis-targeting chimera (PROTAC), that targets BCL-X_L to the Von Hippel-Lindau (VHL) E3 ligase for degradation. We found that DT2216 was more potent against various BCL-X_L-dependent leukemia, lymphoma and cancer cells but considerably less toxic to platelets than ABT263 in vitro because VHL is poorly expressed in platelets. In vivo, DT2216 effectively inhibits the growth of several xenograft tumors including T-cell acute lymphoblastic leukemia and T cell lymphoma as a single agent or in combination with other chemotherapeutic agents, without causing appreciable thrombocytopenia. These findings demonstrate the potential to use PROTAC technology to reduce on-target drug toxicities and rescue the therapeutic potential of previously undruggable targets. Furthermore, DT2216 may be developed as a safe first-in-class antitumor agent targeting BCL-X_L.

Lihong Shi

Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, China

Biography

Dr. Shi received her Ph.D degree in 2008 from Institute of Zoology, Chinese Academy of Sciences majoring physiology. She gained her postdoc training at Prof. Engel's lab at University of Michigan Medical School from 2008 to 2014. After that, she established her lab in institute of Hematology, CAMS/PUMC in Tianjin, China and currently her group focuses on the molecular regulatory mechanism of normal erythropoiesis and the pathogenesis of red cell diseases. She has since published more than 40 papers in scientific journals including Nat Med, Nature Communications, Nucleic Acids Res, PLoS Genet, Bioinformatics et al.

Abstract

Hematopoietic stem cell heterogeneity is associated with myeloproliferative neoplasm

While tissue stem cells are heterogeneous, the implications of this heterogeneity for disease pathogenesis remain poorly understood. The JAK2V617F^{+} myeloproliferative neoplasms (MPNs), harboring the same JAK2 mutation in hematopoietic stem cells (HSCs), display diverse phenotypes, including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). This scenario constitutes an instructive paradigm for analyzing the pathological consequences of stem cell heterogeneity. Single-cell gene expression profiling with parallel mutation detection demonstrated that the megakaryocyte (Mk)-primed HSC subpopulation expanded significantly in ET, and this expansion was driven primarily by JAK2 mutation. This study provides evidence for a paradigm in which the specific pathogenic consequences of a disease mutation are at least in part determined by stem cell heterogeneity.

Defu Zeng

City of Hope, USA

Biography

Dr. Defu Zeng obtained his MD from Fujian Medical University and postdoctoral training in transplantation immunology at Stanford University School of Medicine. Dr. Zeng has been a full professor of Immunology/Hematopoietic Cell Transplantation at the Beckman Research Institute, City of Hope National Medical Center in California since 2013. Dr. Zeng has become an internationally well-recognized leading scientist in the preclinical field of GVHD pathogenesis, prevention and therapy. Dr. Zeng is also a pioneer in the field of induction of mixed chimerism as a curative therapy for hereditary hematological disorders and autoimmune diseases. Dr. Zeng's studies are well funded with two NIH R01 and CIRM clinical trial grants.

Dr. Zeng has >75 high impact publications in Science translational Medicine, Nature communications, JCI, JEM, PNAS, Blood. He has written commentaries for JCI, PNAS and blood, as well as a chapter "Mechanisms of Immune Tolerance" in Thomas Hematopoietic Cell Transplantation, Edition V (2016). Dr. Zeng had been a standing member of NIH study section of transplantation, tolerance, and tumor (TTT) and is now an Ad Hoc reviewer for many NIH study sections. Dr. Zeng also participates in international grant review service in China and Hong Kong.

Abstract

Anti-IL-2 preserves graft versus leukemia activity while preventing graft versus host disease

Donor T cells mediate both graft versus leukemia (GVL) activity and graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (Allo-HCT). Development of methods that preserve GVL activity while preventing GVHD remains a long-sought goal. We reported that depletion of donor $CD4^+$ T cells in transplants early after Allo-HCT augmented alloreactive $CD8^+$ T cell anergy, exhaustion and apoptosis in the GVHD target tissues but not in the lymphoid tissues, leading to prevention of GVHD while preserving GVL activity (*Ni & Song et al: JCI 2017*). We hypothesize that the mechanisms may be through removal of IL-2 help from donor $CD4^+$ T cells for donor $CD8^+$ T cells, and administration of anti-IL-2 mAb can prevent acute GVHD. In the current studies, we found that administration of anti-IL-2 mAb early after Allo-HCT in mice attenuates the severity of acute GVHD while preserving GVL activity that is dramatically stronger than observed with tacrolimus (TAC) treatment that blocks production of IL-2 in T cells. Anti-IL-2 treatment down-regulates activation of IL-2-Stat5 pathway and reduces production of GM-CSF. In GVHD target tissues, enhanced T cell PD-1 interaction with tissue- PD-L1 leads to reduced activation of AKT-mTOR pathway but increased expression of Eomes and Blimp-1, increased T cell anergy/exhaustion, expansion of $Foxp3^+$ Treg and $Foxp3^-$IL-10-producing Tr1 cells, and depletion of GM-CSF-producing Th1/Tc1 cells. In recipient lymphoid tissues, lack of donor T cell PD-1 interaction with host-tissue PD-L1 preserves donor $PD\text{-}1^+TCF\text{-}1^+Ly108^+CD8^+$ T memory progenitors (Tmp) and functional effectors that have strong GVL activity. Anti-IL-2 and TAC treatment have qualitatively distinct effects on donor T cells in the lymphoid tissues, and $CD8^+$ Tmp cells are enriched with anti-IL-2-treatment compared to TAC treatment. Thus, anti-IL-2 treatment early after HCT represents a novel approach for preserving GVL activity while preventing acute GVHD.

Anna Bigas

Institut Hospital del Mar d'Investigacions Mèdiques, Spain

Biography

Anna Bigas holds a Bachelor of Science (1988) and a PhD in Biological Sciences (1993) from the University of Barcelona (Spain). She has a long-standing interest in hematopoietic stem cells, which started in her PhD thesis by characterising human hematopoietic stem cells. She continued her studies in the Fred Hutchinson Cancer Research Center in Seattle. Her pioneering work as a post-doc identified a role of Notch in the regulating hematopoietic differentiation, a highly influential contribution to the field of hematopoiesis (PNAS 1996, Mol. Cell. Biol 1998, Blood 1999)

Since starting her independent research group in Spain, she has sought to decipher the molecular mechanisms that regulate stem cell commitment, maintenance, differentiation and oncogenic transformation, mainly focussed in the hematopoietic and intestinal system. Through refined genetic studies she has demonstrated crucial roles for Notch and Wnt in the generation of hematopoietic stem cells in the mouse embryo (Development, 2005, EMBO J 2008, JEM 2012, 2013, 2014, Nat.Commun 2015, EMBOJ 2020).

Her work also helped identify NFkB and b-catenin as a new therapeutic target for the treatment of T-ALL (Cancer Cell 2010, Leukemia 2016), thus contributing to the molecular understanding of this disease. In addition she has actively participated in identifying novel functions for specific NFkB elements other systems (PNAS 2004, 2007, 2009; Cell Reports 2012, Cancer Cell 2013, Leukemia 2018, Mol Cell 2019, EMBO Rep 2020).

She is currently a research group leader at IMIM in Barcelona and the scientific director of CIBERONC, a national cancer research collaborative network.

Abstract

Notch ligands orchestrate the generation of Hematopoietic Stem Cells in the embryo

A conserved Notch function is crucial for the specification and generation of Hematopoietic Stem Cells (HSC) across evolution. By using genetically modified organisms, most of the elements that are functionally relevant have been identified mainly in mouse and zebrafish. However, due to the disruptive nature of these studies, it is still uncertain the physiological sequence of events that lead to and result from this specific Notch function. This is especially important in terms of reproducing this activity in vitro. The Notch system provides cells with a binary decision mechanism that takes place among neighboring cells. In vertebrate systems, several Notch ligands and receptors co-exist in the same cell and cells compete for activating the Notch receptor that will condition the fate of that cell.
In the Aorta-Gonad-Mesonephros (AGM) region, HSCs develop from hemogenic endothelial cells that reside in the ventral side of the dorsal aorta. Cells in the developing aortic endothelium co-express different types of Notch ligands and receptors. Several groups including ours have contributed to define the elements involved in this pathway, but still several gaps prevent to have a complete understanding. In addition to the Notch1 receptor, Jagged1 and hes1, we have recently shown how Dll4 has also an important structural function in the hematopoietic cluster composition of the aorta. We provided data on how blocking Dll4 with a specific antibody impinges on the number of cells recruited into the cluster and the HSC activity. However, how to integrate all these different signals coming from Dll4 and Jagged1 in the same or different hemogenic/hematopoietic cells is complex. Thanks to current reagents and methodologies, we can now assess the transcriptome of cells expressing different ligands and receptors and define the ones that activate Notch from the other ones. Our aim is to understand the Notch pathway at a cellular level in the hemogenic and hematopoietic cells of the AGM.

Claudia Waskow

Leibniz Institute on Aging, Germany

Biography

The aim of my studies is the identification of cell-autonomous and -extrinsic factors governing maintenance and differentiation of hematopoietic stem cells and function of immune cells from mice and men over time. This includes the understanding of immune cell homeostasis, e.g. their generation and turn-over during steady-state and under inflammatory and infectious conditions in young adults and during the aging process. The research of my laboratory, thus, focuses on uncovering basic mechanisms that regulate immune cell biology in the young and elderly, and this understanding may pioneer novel translational approaches.

Abstract

Engraftment of functional human hematopoietic stem cells in mice.

Xenotransplantation models allow for in-depth analysis of human hematopoietic stem cell (HSC) and immune cell function in vivo. We generated novel mouse models supporting stable human HSC engraftment, which is a prerequisite for the continuous generation of all adult human hematopoietic cell types in mice. By introducing a loss-of-function Kit receptor into NSG mice we generated NOD/SCID Il2rg-/- KitW41/W41 (NSGW41) mice that combine an impaired endogenous HSC compartment with immunodeficiency that efficiently support stable engraftment of human HSCs in the long-term without the need for any conditioning therapy. As a consequence, multilineage engraftment including cells of the myeloid and erythroid lineages is highly improved in NSGW41 mice. Mechanistically, endogenous murine HSCs with a defective Kit receptor are largely replaced by human Kit-proficient donor HSCs. Further, ‘humanization’ results in quantitative and qualitative changes of the mouse bone marrow microenvironment, suggesting that a mutual cross-talk between human HSCs and the mouse stem cell niche takes place. Using these novel recipient mice we attempt to improve the outcome of xenotransplantation of islet cells by shaping the immune response in the surrogate humanized host.

Elisa Laurenti

University of Cambridge, UK

Biography

Dr Elisa Laurenti's career in cell biology has focused on studying haematopoietic stem cells (HSCs) first using mouse models during her PhD with Prof. Andreas Trumpp in Lausanne, then with Dr John Dick in Toronto during her post-doctoral studies. There she established robust methods to study the function and molecular make-up of human HSCs. In 2014, she moved to the Cambridge Stem Cell Institute where she established my own laboratory thanks to a Wellcome – Royal Society Sir Henry Dale Fellowship. Her research aims to understand how HSC function is regulated at all stages of human life to eventually improve treatment of blood diseases. More specifically, her laboratory currently focuses on i) understanding how the functional output of the human HSC pool changes over a human lifetime, at steady-state and under inflammatory conditions; ii) characterising the molecular regulation of quiescence and its relevance to HSC ex vivo expansion and gene therapy.

Abstract

Human haematopoietic stem and progenitor cell landscapes: location matters

In adults, most hematopoietic stem and progenitor cells (HSPCs) reside within the bone marrow (BM), giving rise to all mature blood cells. Yet at any given time, a small proportion of HSPCs circulates in peripheral blood (PB), and under severe stress and disease, the spleen can significantly contribute to blood production. However, the cellular, molecular and functional composition of circulating and extramedullary HSPC pools remains unexplored. Here I will discuss the single cell characterisation of the adult human HSPC pool found in spleen and non-mobilised PB, comparing and contrasting it to BM. Using matched and unmatched samples from deceased and living donors, we profiled more than 50,000 single CD34+ HSPCs by scRNA-seq and 3,900 single phenotypic haematopoietic stem cells / multipotent progenitors (HSC/MPPs) in functional assays. In BM, we find a topography of the hematopoietic hierarchy that supports continuous HSPC proliferation and blood production. In contrast, the cellular configuration in extramedullary tissues is positioned for lineage-primed demand-adapted haematopoiesis, including a molecularly distinct subset of HSC/MPPs not found in BM. PB HSC/MPPs sustain a unique differentiation potential and configuration in healthy conditions, but which become imbalanced with age and in haematological conditions. Overall these data identify extramedullary cellular reservoirs for demand-adapted haematopoiesis and provide a framework of clinical relevance.

Bisen Ding

Sichuan University，China

Biography

Dr. Bi-Sen Ding is a distinguished investigator at Sichuan University. He received his bachelor from Nanjing University and Ph.D. in Pharmacology from the University of Pennsylvania. His research aims to uncover microenvironmental regulation of organ regeneration and fibrosis. During his Ph.D. study at PENN and postdoc research at Howard Hughes Medical Institute/Cornell University, he elucidated that vascular endothelial cell produces paracrine factors to instruct liver and lung regeneration and repair, functionalizing a "vascular niche". These findings were published with him as first author in journals such as “Cell”, “Nature”, “Blood”, and “Circulation”. Dr. Ding initiated his independent research as tenure track Assistant Professor at Cornell in 2013. Since then, his lab has uncovered that the pro-regenerative cues from vascular endothelial cell can be subverted to promote fibrosis or tumorigenesis. Therapeutic targeting of this “maladaptive vascular niche” can enable clinical strategy to promote organ regeneration and to block fibrosis and tumorigenesis. His ongoing research has further demonstrated that perivascular hematopoietic and fibroblast cell regulate the vascular niche in a divergent manner, differentially promoting either regeneration or fibrosis/tumorigenesis in injured organs. These findings are published in “Nature”, “Cancer Cell”, “Nature Cell Biology”, “Nature Medicine”, “Science Translational Medicine”, and “Developmental Cell” communicated as corresponding author.

Abstract

Decoding the heterogenous vascular niche in lung regeneration

Our research goal is to coax the damaged organ to regenerate and bypass fibrosis. Upon injury, organs such as liver and lung undergo regeneration and sometimes scarring. Overwhelming scarring constantly causes irreversible fibrosis in injured organs at the expense of regeneration. We are focused on illustrating how blood and vascular cells form an instructive microenvironment (as "hematopoietic-vascular niche") to jointly control organ regeneration and fibrosis. We have uncovered that blood and vascular cells produce epithelially active factors in the damaged organs to regulate the fate of facultative stem cells. Unfortunately, this pro-regenerative signaling landscape of hematopoietic-vascular niche is frequently overturned in diseased organs, leading to fibrosis and sometimes tumorigenesis. Therefore, we aim to decode the cellular and molecular mechanism involved in the dynamic crosstalk between hematopoietic-vascular niche, parenchymal stem/progenitor cells, and mesenchymal cells in organ repair. Building on these mechanistic studies, we seek to design regenerative therapy approach to stimulate fibrosis-free organ repair, especially by editing the hematopoietic-vascular niche to facilitate the engraftment of transplanted parenchymal stem cells.

Reinhold J. Medina

Queen's University Belfast, UK

Biography

Reinhold completed his medical training and obtained his MD from San Agustin University-Peru in 2000. He was awarded his PhD in Stem Cell Biology from Okayama University Medical School, Japan in 2006. He was then recruited to Queen's University Belfast, UK. After two consecutive postdoctoral fellowships from JDRF International and Fight for Sight in 2008 and 2010 respectively, he was appointed Lecturer in 2012, promoted to Senior Lecturer in 2017, and Professor in 2020. Reinhold has a keen interest in understanding basic science to explain disease. His work on human endothelial progenitor cell biology is internationally recognised. His research focusses on the development of a stem cell therapy for regeneration of blood vessels with important implications for diabetic vascular complications. Reinhold's research team work on vascular stem cell biology could lead to meaningful new approaches for the treatment of diabetic vascular complications.

Abstract

Developing cell therapies for vascular repair in diabetes

Diabetes remains a major health problem worldwide. Although there have been significant advances in hyperglycemia management, morbidity and mortality related to diabetic complications remain high. Diabetic complications include atherosclerosis, retinopathy, and nephropathy. Their pathogenesis is driven by hyperglycemia-induced damage of endothelial cells and pericytes leading to hypoxia, ischemia, and tissue dysfunction. Therefore, diabetes has been considered as a disease of blood vessels. A suggested logical approach to avoid diabetic vascular complications is to promote vascular repair; however, endogenous vasoreparative cells in diabetic patients have been demonstrated to be impaired in number and function. Our research has identified a subtype of endothelial progenitor cells known as endothelial colony forming cells (ECFCs) as an ideal candidate to develop cell therapies to revascularize ischemic tissues in diabetic patients. ECFCs are consistently isolated from umbilical cord blood, have a well-defined immunophenotype CD31+CD146+CD45-CD14-, and exhibit diploid normal karyotypes. ECFCs unequivocal endothelial phenotype was proven by transcriptomics. ECFCs possess single cell clonogenic capacity, and effectively form vascular networks in vitro and in vivo. Importantly, ECFCs capacity for vascular repair has been demonstrated in several preclinical animal models of tissue ischemia. Our evidence shows that ECFCs revascularize the murine ischemic retina and therefore hold potential for treating early stages of diabetic retinopathy.

Jiaxi Zhou

Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, China

Biography

Dr Jiaxi Zhou is a principle investigator and associate director of State Key Laboratory of Experimental Hematology, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Perking Union of Medical College. He obtained his PhD from the Graduate School of Chinese Academy of Sciences in 2004 then received the postdoctoral training at the Stowers Institute for Medical Research and University of Illinois at Urbana-Champaign from 2005-2010. He joined the SKLEH as a group leader in the end of 2010. Dr. Jiaxi Zhou's laboratory has a long-term interest in the study of early hematopoietic differentiation, generation of megakaryocytes (MKs) and platelet from human pluripotent stem cells as well as hematopoietic disorders modelling with hPSCs. His group recently have successfully captured the human MKs both in vivo and in vitro and identified their transcriptome in single cell solution. Novel markers and functional heterogeneity of human MKs were characterized. Highly efficient strategy for derivation of HPC as well as MKs and platelet in large-scale was developed base on this knowledge.

Abstract

Revealing Cellular Heterogeneity, Developmental Trajectory and Novel Subpopulations with Immune Functions in Megakaryocytes

Megakaryocytes (MKs) and their progeny platelets function in a variety of biological processes including coagulation, hemostasis, inflammation, angiogenesis and innate immunity. However, the divergent developmental and cellular landscape of human MKs remains mysterious. Here, by deriving the single-cell transcriptomic profiling of MKs from human yolk sac (YS), fetal liver and adult bone marrow, we unveiled cellular heterogeneity within MKs and identified a MK subpopulation with high enrichment of immune-associated genes. We analyzed cells that recapitulate distinct developmental stages of human megakaryopoiesis and captured the dynamic transcriptomic landscape at the single-cell resolution. We also found that the MK subpopulation enriched with immune-associated genes is present at the various developmental stages and is generated along a unique trajectory from MK progenitors. Furthermore, we identified two surface markers, CD148 and CD48, for mature MKs with immune characteristics, allowing us to define a novel CD148+CD48+ MK subpopulation with immune potency. At the functional level, these CD148+CD48+ MKs can respond rapidly to immune stimuli both in vitro and in vivo, exhibit high-level expression of immune receptors and mediators, and might function as immune sensors and recruit immune cells to the peripheral blood to participate in immune regulation. Our findings uncover cellular heterogeneity and a novel immune subset of MKs and should greatly facilitate the understanding of the divergent functions of MKs.

Anna Krasnodembskaya

Queen's University Belfast, UK

Biography

Dr Anna Krasnodembskaya holds a Reader (Associate Professor) post at the Wellcome-Wolfson Institute for Experimental Medicine, Queens University of Belfast, UK and leads a group of postdoctoral researchers, PhD, Masters' and undergraduate students. Her studies are focused on the development of Mesenchymal Stem Cells- based therapies for Acute Respiratory Distress Syndrome and investigation of the mechanisms mediating MSC effect. Ongoing work is investigating the role of mitochondrial dysfunction in the pathogenesis of ARDS and the ability of MSC-derived extracellular vesicles to alleviate it through transfer of healthy mitochondria and miRNAs.

Dr Krasnodembskaya earned her Masters and then Doctorate in Biology at St. Petersburg State University, Russia. She was selected to be a member of Postdoctoral Fellowship Program and was appointed as Assistant Professor at the School of Biological Sciences. She then conducted her second postdoctoral training at the University of California, San Francisco in Professor Michael Matthay's laboratory, before joining the Faculty at Queen's University of Belfast in 2013, she was promoted to a Reader post in 2019. Anna has nearly 10 years' experience in pre-clinical MSC research and her studies have informed the design of several clinical trials for MSC in ARDS and sepsis in USA, Canada and UK. Her publications in Stem Cells, 2010, Thorax and AJPLung, 2012 are recognised as seminal papers in the field (>500 citations). Her publication in Stem Cells in 2016 was recognised as the most impactful paper of the journal in 2016 and Anna was named Stem Cells Young Investigator of 2017. Her ongoing research is funded by UK Medical Research Council (PI on 3 Research Grants, >£1M in total) and Wellcome Trust.

Abstract

Mitochondrial transfer by mesenchymal stem cells as a strategy for lung repair

Acute Respiratory Distress Syndrome (ARDS) is a major cause of acute respiratory failure in critically ill patients requiring mechanical ventilation, with no effective treatment and is associated with high mortality and morbidity. Mitochondrial dysfunction and its potential mechanistic role in the evolution of lung diseases have become increasingly recognized as an important and translationally promising research field. Strategies aiming to protect mitochondria from injury or to enhance biogenesis are being actively explored as potential therapeutic opportunities.

Mesenchymal Stem/Stromal Cells(MSCs)-based therapy is considered as a promising approach for ARDS because of their ability to target major aspects of ARDS pathophysiology. MSCs act through both cell contact-dependent regulation of the host cells and by secreting soluble factors and extracellular vesicles. Direct intercellular communication between MSCs and their target cells can occur through formation the tunnelling nanotubules leading to direct exchange of cytoplasmic content (including organelles such as mitochondria and lysosomes) and resulting in the restoration of function of the host cells injured by disease microenvironment. More recently, MSC-derived extracellular vesicles (EVs) have attracted significant attention as potent means of intercellular communication and it has been demonstrated by several groups (including our studies) that MSC EVs also are able to carry mitochondria. Transfer of healthy MSC derived mitochondria to epithelial cells has been associated with remarkable therapeutic efficacy in models of acute lung injury and asthma, we have demonstrated that mitochondrial transfer resulted in metabolic reprogramming of primary human macrophages towards anti-inflammatory phenotype with enhanced phagocytic activity. MSC modulation of macrophages through mitochondrial transfer also was critical for immunomodulatory and antimicrobial effects of MSCs in the models of LPS and E.coli-induced acute lung injury. Furthermore, we have recently found that MSC EV mediated mitochondrial transfer is a novel mechanism of promoting human distal lung epithelial repair. Our ongoing work is investigating the role of mitochondrial dysfunction in the impairment of alveolar-capillary barrier in ARDS and the ability of mitochondrial transfer mediated by MSC-derived extracellular vesicles to alleviate these.

John Wagner

University of Minnesota, USA

Biography

John Wagner MD, Professor of Pediatrics, Director of the Institute of Cell, Gene and Immunotherapy and founding member of the Stem Cell Institute, is a clinical and translational investigator in the field of hematopoietic stem cell transplantation and immune cell therapies with more than 30 years of experience leading phase I/II/III clinical studies in the treatment of malignant disorders and rare genetic diseases. He is most well-known for the development of umbilical cord blood as a source of transplantable stem cells, performing the first transplant with cord blood in a child with leukemia in 1990. He subsequently developed the double umbilical cord blood platform that markedly increased the utilization of this stem cell source in the treatment of adults with hematological malignancies. His current research is focused on hematopoietic stem cell expansion using a aryl hydrocarbon receptor antagonist to speed engraftment after transplant, regulatory T cells to control graft-versus-host disease, thymic progenitors to enhance immune recovery. In addition, he pioneered the use of hematopoietic stem cell transplant as a vehicle for extracellular matrix repair in the treatment of severe forms of epidermolysis bullosa and improved survival in children and adults undergoing transplant for Fanconi anemia.

Abstract

Hematopoietic Stem Cell Expansion: Developmental Pathway and Clinical Results

Hematopoietic stem cells (HSCs) are defined by their capacity of self-renewal and multipotency. It has previously been shown that nearly all repopulating capacity can be found in the CD34+CD90+ cell population. In recent years, the use of autologous and allogeneic HSCs has not only increased in the treatment of patients with refractory or relapsed lympho-hematopoietic malignancy but also in various non-malignant diseases, including the use of gene modified autologous HSC for selected inherited disorders. As limited quantities of HSCs are available from some donors, e.g., umbilical cord blood (UCB), or after gene modification of autologous HSC, there has been considerable interest in the development of ex vivo expansion methods. High-throughput screening of thousands of molecules has identified several with HSC expansion potential; these include prostaglandin E2 (PGE2), UM171, a pyrimido-indole derivative, and StemRegenin 1 (SR1), an aryl hydrocarbon receptor (AHR) antagonist. The aim of our initial studies was to determine safety of the SR1 first in the setting of a double UCB transplant, with one unit unexpanded to minimize the risk of graft failure should SR1 culture lead to terminal differentiation of all HSC. Subsequent studies have focused on efficacy as well as evaluating the effect of using smaller but better HLA matched UCB units as starting material, considering the 350-fold expansion potential of CD34+ cells with AHR antagonists. The presentation will detail the developmental pathway to the clinic, current results and next generation studies using expanded HSC, such as for manufacturing thymic progenitors to reduce the period of immune incompetence universally observed after allogeneic HSC transplantation.

Dan Kaufman

University of California San Diego, USA

Biography

Dr. Kaufman is a Professor in Department of Medicine, Division of Regenerative Medicine and Director of the Cell Therapy program at the University of California-San Diego. Dr. Kaufman does clinical work in hematology/BMT. His research focuses on use of human pluripotent stem cells to study development of hematopoietic stem/progenitor cells, lymphocytes, and other mesodermal lineages. In particular, his studies have developed efficient means to produce natural killer cells from human ES cells and iPSCs suitable for new clinical applications to treat relapsed/refractory cancers- both hematologic malignancies and solid tumors. Current studies aim to translate use of these cells into clinical therapies and to engineer these NK cells with receptors to improve killing of cancer cells.

Abstract

Use of human pluripotent stem cells to identify novel regulators of immune cell activity

Human pluripotent stem cells provide a key resource for cellular immunotherapies. Studies from our group have demonstrated that natural killer (NK) cells can be efficiently derived from both human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), which can be engineered to better target refractory malignancies. hESCs and iPSCs serve as a platform to express chimeric antigen receptors and other modifications to enhance anti-tumor activity. Importantly, hESC/iPSC-derived NK cells can be expanded to clinical scale in current GMP-compatible conditions. Since NK cells function as allogeneic cells, this strategy enables use of hESC/iPSC-derived NK cells as an “off-the-shelf” targeted cellular immunotherapy against refractory malignancies. Additional work from our group has done a CRISPR/Cas9-mediated screen of tumor cell lines to identify novel regulators of NK cell-mediated activity. These studies demonstrate deletion of a gene that regulates tumor cell production of exosomes can lead to enhanced NK cell-mediated killing, suggesting a novel strategy to improve anti-tumor cell-based therapies.

Shijiang Lu

HebeCell, USA

Biography

Shi-Jiang (John) Lu, PhD, MPH, is currently the President and CEO of HebeCell Corporation, focusing on the development and clinical translation of regenerative medicine and cell therapy technologies, especially iPS-CAR-NK cells for the treatment of cancer, autoimmune and viral infectious diseases. Before establishing HebeCell, he was the Senior Director of Research at Advanced Cell Technology/Ocata Therapeutics. Dr. Lu is an expert in stem cell biology and regenerative medicine with 20 years of experiences. He has been conducting translational researches and discovery of novel therapeutic strategies utilizing human embryonic stem cells (hESC), induced pluripotent stem cells (iPSC) and their derivatives. The goal of his research is to generate hESC/iPSC-derived products for the treatment of human diseases. He also has extensive experience in process development and large-scale production of human PSC derivatives under defined conditions for clinical trials. Dr. Lu is the inventor of more than 20 patents in stem cell field: in an analysis of global stem cell patent landscape by Nature Biotechnology in 2014, Dr. Lu's patent application and citation ranked No. 7 and No. 5, respectively. In addition to stem cell research, Dr. Lu also has more than 10 years experiences in cancer research. Dr. Lu received his BS degree from Wuhan University (1982), MS degree from Peking Union Medical College (1985), MPH degree from Columbia University (1988) and PhD degree from University of Toronto (1992).

Abstract

CAR-NK cells from Engineered Pluripotent Stem Cells: Off-The-Shelf Therapeutics for All Patients

Despite the rapid advancement of immune therapies utilizing NK cells, the manufacture of high quality NK cells at industrial scale remains a major technical challenge. Unlike donor sourced NK cells, human pluripotent stem cells (PSCs) offer an unlimited renewable source for NK cells. At HebeCell, we developed a novel 3D-bioreactor platform that is capable of producing high quality NK cells in industrial scale. More importantly, our 3D platform mimics the environments of secondary lymph tissues with continuous release of NK cells from these 3D spheres without stimulation of feeder-cells, thus eliminating the process of exhaustive NK expansion that often compromises the potency of immune cells. First, CAR-constructs were introduced into human iPSCs and stable and permanent CAR-iPSC clones were established. Secondly, CAR-iPSCs in 3D spheres were converted to hemogenic endothelial progenitors. By switching to conditions favouring sustained lymphopoiesis and NK cell development, large quantity of NK cells were released from spheres mimicking lymphoid organs. Up to 2.5 billion high purity iPS-NK cells (~95% CD56+) were harvested from one 500 ml bioreactor. These iPS-NK cells killed a variety of cancer cells including both blood and solid tumours such as pancreatic, ovarian and breast cancer cells in vitro, as well as multiple viral infected cells. In summary, our new platform offers a viable alternative strategy for the manufacture of pure and potent NK cells at scales that meet the demand of unlimited doses of allogeneic off-the-shelf therapeutics for all patients.

Xiaohua Shen

Tsinghua University, China

Biography

Xiaohua Shen is a Cheung Kong Scholar, associate professor in the School of Medicine and an associate investigator in the Center of Life Sciences at Tsinghua University. Her major research interest is to understand how the non-coding portions of the genome influence chromatin structure, gene expression, and stem-cell fate in development. In the past years, the Shen lab has rigorously investigated novel aspects of ncRNAs, genomic repeats, and RNA-binding proteins (RBPs) in the regulation of transcription, chromatin and genome organization. Her work facilitates the functional inference of ncRNA genes, and brings about a paradigm shift in our understanding of RNA and the noncoding genomes in transcription and chromatin regulation.

Abstract

RNA-binding proteins harness RNA and phase separation to modulate transcription in pluripotent stem cells

Much of the developmental complexity of higher eukaryotes is thought to arise from gene regulation. RNA represents a hidden layer of regulatory information in complex organisms. I will discuss our recent progress in exploring novel functions of RNA-binding proteins in the regulation of transcription and chromatin states in pluripotent stem cells.

Feng Liu

Institute of Zoology, Chinese Academy of Sciences, China

Biography

Feng Liu received his PhD in biological sciences from the Institute of Genetics and Developmental Biology, Chinese Academy of Sciences in 1999 and then conduced postdoc training in National University of Singapore, Vanderbilt University Medical School, and Weatherall Institute of Molecular Medicine in University of Oxford, from 2000 to 2008. In 2009, he was appointed as Professor of Cell Biology in the Institute of Zoology, Chinese Academy of Sciences. The Liu laboratory is mainly focused on hematopoietic stem cell (HSC) development, using both zebrafish and mouse models. We are studying molecular mechanisms of HSC emergence and maintenance (expansion and differentiation) including the key signal transduction pathways, gene regulatory network and epigenetic modifications, to better understand programming/reprogramming of these cells for potential therapeutic application.

Abstract

Deciphering new mechanisms of HSC fate determination in vertebrates

The hematopoietic system is a paradigm for stem cell research. Hematopoietic stem cells (HSCs) are a population of multipotent cells that can self-renew and differentiate into all blood lineages. The development of HSCs and their derivatives must be tightly controlled, which involves a complex of extrinsic signaling and intrinsic factors. Studying regulatory mechanisms of developmental hematopoiesis in vivo in zebrafish and mouse models has greatly facilitated our understanding of HSC biology in vertebrates. I will talk about our recent new findings on HSC development, which may help to design new strategies for the generation and/or expansion of transplantable and functional HSCs in vitro.

Ping Zhu

Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences, China

Biography

Ping Zhu is an associate professor at institute of hematology and blood disease hospital in Tianjin, China, since he finished hist Ph.D. training at professor Fuchou Tang's lab at Peking University. Zhu's lab focuses on the study of cell identity determination, fate choice and trajectory routes during differentiation in the hematopoietic system. The lab combines single-cell multi-omics techniques, including levels at the genome, transcriptome and epigenome scale, and computational analysis to dissect the molecular basis underlying these focused issues in both homeostasis and diseases. Another research interest is to develop computation tools to facilitate the biological insights mining for huge volumes of sequencing data.

Abstract

Single-cell Transcriptomes of Blood Cells and Beyond

Blood cells are crucial for the maintenance of hematopoietic system and support for lifelong homeostasis. Single-cell transcriptome profiling approaches offer new dimensions for determining the identities of blood cells in addition to regular immunophenotypes and retrospective functions. To facilitate the study of physiological and pathological hematopoiesis, we construct the transcriptional atlas of blood cells in both human and mice by in-depth sequencing of immunophenotype-enriched hematopoietic stem/progenitor cells and mature cells from different lineages. Furthermore, by taking the atlas as references, we study the hematopoiesis regeneration upon HSC transplantation in mice and bone marrow failure in human. Notably, differentiation of HSC rather than expansion of HSC is observed immediately after transplantation. We also uncover the cellular and molecular basis of immune attack leading to pancytopenia and provides potential targets for therapy to improve hematopoiesis. In summary, the transcriptional atlases of human and mice blood cells are established and applied to the studies of HSC transplantation and bone marrow failure. We anticipate that these atlases of blood cells would serve as valuable resources for the in-depth study of hematopoiesis (http://scrna.sklehabc.com).

Shai Izraeli

Tel Aviv University, Israel

Biography

I am a physician scientist who focuses on translational laboratory-based of pediatric hematological malignancies and on cancer predisposition syndromes. My vision is to promote innovation by integrating multidisciplinary basic, translational and clinical research to improve the care of children with cancer. I am particularly interested in studying developmental aspects of childhood leukemia. Over the last decade we have focused on leukemia predisposition syndroes in particular Down Syndrome. We discovered a subtype of high-risk ALL characterized by mutational activation of the JAK-STAT pathway (Lancet 2008, JEM 2011, Blood 2010, 2014, PNAS 2017). These discoveries have led to ongoing clinical trials of the children oncology group with JAK inhibitors for pediatric ALL. More recently we have focused on the metabolic adaptation of ALL to their micronvironment especially the central nervous system (Nature Cancer, in press) and in the role of signaling and transcriptional regulation in normal and malignant hematopoiesis. These studies have been funded by multiple national and international grants and have involved multiple national and international collaborations in both basic and clinical research with scientists and clinicians in North America, Australia, Japan and Europe.

Clinically I am the chair of the Division of Pediatric Hematology and Onclology in the Schneider Children's Medical Center of Israel, also affiliated to Tel Aviv University. We are leading the ALL trials in Israel as part of the European BFM-AIEOP group. Internationally I have been involved in leading position in several hematology and cancer organizations. Most significantly, I am a member of the executive Board of the European Hematology Association (EHA), the previous chair of Biology and Diagnosis of the international BFM childhood leukemia group, the biology and clinical committees of the International Treatment of Children with Cancer (ITCC) and the co-chair of the biology committee of TACL, USA.

Abstract

An instructive role for IL7RA in the development of human B-cells and B cell precursor leukemia.

B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is preceded by a clinically silent pre-leukemia. Experimental models that authentically re-capitulate disease initiation and progression in human cells are lacking. We previously described activating mutations in interleukin 7 receptor alpha (IL7RA) that are associated with the poor-prognosis Philadelphia-like (Ph-like) subtype of BCP-ALL. Whether IL7RA signaling has a role in initiation of human BCP-ALL is unknown.

IL7RA is essential for mouse B-cell development; however, patients with truncating *IL7RA* germline mutations develop normal mature B-cell populations. Herein, we explore the consequences of aberrant IL7RA signaling activation in human hematopoietic progenitors on malignant B-cell development.

Transplantation of human cord-blood hematopoietic progenitors transduced with activated mutant IL7RA into NOD/LtSz-*scid IL2Rγnull* mice resulted in B-cell differentiation arrest with aberrant expression of CD34+ and persistence of pro-B cells that survive despite failing to achieve productive rearrangement of immunoglobulin V(D)J gene segments. Activation of IL7RA signaling enhanced self-renewal and facilitated the development of a BCP-ALL in secondary transplanted mice. The development of leukemia was associated with spontaneous acquired deletions in CDKN2A/B and IKZF1 similar to what is observed in Ph-like BCP-ALL in humans. Single cell gene expression analysis suggested that pre-leukemic cells resided within a subpopulation of early B-cell precursors with CD34+CD10highCD19low immunophenotype.

The development of a bona fide BCP-ALL from IL7RA transduced cells supports the hypothesis that aberrant activation of the IL7RA pathway in human B-cell lineage progenitors has an instructive role by creating a pre-leukemic state which is vulnerable to transformation. These are the first demonstrations of a role for IL7RA in human B-cell differentiation and of a de-novo Ph-like BCP-ALL development from normal human hematopoietic progenitors in vivo.

Wensheng Wei

Peking University, China

Biography

Wensheng Wei received his bachelor degree in Biochemistry from Peking University, Ph.D. in Genetics from Michigan State University. After postdoctoral training and working as a research associate at Stanford University School of Medicine, Dr. Wei became a principle investigator in the School of Life Sciences at Peking University from 2007. He is now a professor of Biomedical Pioneering Innovation Center (BIOPIC), Beijing Advanced Innovation Center for Genomics (ICG), Peking-Tsinghua Center for Life Sciences (CLS), State Key Laboratory of Protein and Plant Gene Research, and School of Life Sciences at Peking University.

The research of Wei group is mainly focused on the development of eukaryotic gene editing tools, with the emphasis on the high-throughput functional genomics and gene therapy. The combination of forward and reverse genetic means are employed, often in a high-throughput fashion, for the understanding of the molecular mechanisms underlying human diseases, including cancer and infection.

Abstract

Gene Editing and High-throughput Functional Genomics

We have previously developed a series of high-throughput screening (HTS) methods based on CRISPR/Cas9 system for the functional identification of protein-coding genes and long non-coding RNAs. We have also re-designed sgRNA scaffold that greatly boosts the efficiency and data quality for HTS. Our recent efforts include the identification of functional 3D-hubs that were essential for cell viability, the development of a new approach for mapping functional sites of protein of interest at single amino acid resolution, and a series of novel high-throughput strategies derived from base editors. Besides these high-throughput strategies to facilitate the accurate and rapid identification of functional genomic elements in various settings, we have recently developed a novel programmable RNA editing strategy called LEAPER. Unlike conventional nucleic acid editing technology that requires simultaneous delivery of editing enzymes (such as Cas protein) and guide RNAs into cells, LEAPER enables precise and efficient RNA editing by recruiting endogenous cellular deaminase using engineered RNAs.

Liran Shlush

Weizmann Institute of Science, Israel

Biography

During his postdoctoral research, Dr. Shlush examined genes commonly mutated in acute myeloid leukemia (AML), successfully identifying those “pre-leukemic” stem cells that go on to form cancerous cells. In his more recent work, Dr. Shlush used population-wide medical data available through a large repository of electronic health records (the Weizmann-Clalit project), along with deep sequencing techniques, to characterize the genes frequently mutated in the peripheral blood cells of individuals who later developed AML. Not only did this work form the basis of a model that accurately predicted AML-free survival, it also led to a model for identifying healthy individuals who are at risk for developing AML in the future. This research by Dr. Shlush and his colleagues represents a paradigm shifting in AML, which has long been considered as an unpredictable and unpreventable disease. It will also generate an enthusiasm toward the possibility of AML prevention through early intervention in a high-risk population.

Abstract

The aging of the blood system

The ability to prevent diseases should be the number one goal of medical research. As humans age, their diseases become more complex (multifactorial) and, accordingly early diagnosis and prevention become strikingly complicated. Our work and the work of others provide an evidence that the age of the blood system as reflected by the accumulation of mutations in hematopoietic stem and progenitor cells (HSPCs), also termed age related clonal hematopoiesis (ARCH) is correlated with both leukemia and cardio vascular disease (CVD). As the ageing of the blood system occurs many years before these diseases it becomes feasible to use parameters of the aging blood in a personalized matter to predict leukemia and CVD.

Yi Zeng

Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, China

Biography

Yi Arial Zeng did her PhD at Simon Fraser University in Canada and postdoctoral work at Stanford University. She has been a principal investigator at Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences since 2010.

Her research interest is to understand the regulatory mechanisms of adult stem cells in various tissues, and the interaction between stem cells and their niche. She has focused her efforts on Procr (protein C receptor), which a target of Wnt signaling, and has been established as a surface marker of adult stem cells in multiple tissues, including the mammary gland, the blood vessel endothelium, the hematopoietic system, and the ovarian epithelium. Her recent work demonstrates that Procr also marks the long-sought pancreatic islet stem cells.

The long-term goal of her research is to determine how the stem cell regulatory mechanisms have deviated in diseases, and to learn how to control the players in these machineries in vivo, as well as to provide ever-expanding stem cells in vitro for the purpose of regenerative medicine.

Abstract

Identify Pancreatic Islet Resident Progenitors

It has generally proven challenging to produce functional β cells *in vitro*. Here, we describe a novel Procr$^+$ cell population in adult mouse pancreas through scRNAseq. The cells reside in islets, do not express differentiation markers and feature epithelial-to-mesenchymal transition (EMT) characteristics. By genetic lineage tracing, Procr$^+$ islet cells undergo clonal expansion and generate all four endocrine cell types during adult homeostasis. Sorted Procr$^+$ cells, representing ~1% of islet cells, can robustly form islet-like organoids when cultured at clonal density. Exponential expansion can be maintained over long time periods by serial passaging, while differentiation can be induced at any time point in culture. Beta cells dominate in differentiated islet organoids, while α, δ and PP cells occur at lower frequencies. The organoids are glucose-responsive and insulin-secreting. Upon transplantation in diabetic mice, the organoids reverse disease. These findings demonstrate that the adult pancreatic islet contains a population of Procr+ endocrine progenitors.

Benjamin Dekel

Tel Aviv University, Israel

Biography

Prof Benjamin Dekel MD, PhD is the Director of the Pediatric Stem Cell Research Institute and the Chief of the Division of Pediatric Nephrology at the Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center. He is a Full Professor of Pediatrics, Human Genetics and Biochemistry and leads the Pediatric Research Center on Genes, Development and Environment at the Sackler School of Medicine, Tel Aviv University. He received a BSc and MD degrees from the Technion and a PhD from the Weizmann Institute of Science, all with highest honors. He completed a Pediatric Residency at Sheba, Post-Doctoral fellowship in stem cell biology at the Weizmann and a Pediatric Nephrology Fellowship at the Schneider Medical Center. Prof. Dekel served as a visiting Professor at the Institute of Stem Cell Biology, Stanford University.

He is known internationally as one of the most innovative and highly recognized investigators in the field of human renal stem cell biology, cell therapy and renal regenerative medicine. In the field of human kidney development and pediatric renal cancer, Prof. Dekel has pioneered the identification of human stem/progenitor cells and their use in tissue repair, regeneration and targeted cancer therapy. Some of his bench research identifying and targeting the renal cancer stem/initiating cell pool has been translated to clinical trials for relapsing kidney cancer in children. Moreover, Prof Dekel is moving towards the translation of his basic research in renal regenerative medicine, which applies novel modalities of cellular therapies with nephron progenitors, to bedside. This tremendous effort may allow kidney patients to delay the need for dialysis and shorten the ever-growing waiting list for a kidney transplant.

Prof Dekel is an elected member of the American Society of Clinical Investigation (ASCI), the American Society of Pediatric Research (APS/SPR) and was recently elected as an inaugural member of the Israel Academy of Scientific Medicine. Prof Dekel has received multiple awards among which are the Youdim Prize for Excellence in Cancer Research and the Israel Medical Association Prize for Medical-Scientific Innovation.

Abstract

Epithelial cell therapies for kidney disease

The generation of nephrons in fetal life depends on the differentiation via a mesenchymal to epithelial transition (MET) of self-renewing, tissue-specific stem cells that give rise to different types of nephron epithelia and are confined to a specific anatomic niche in the nephrogenic cortex. Importantly, these cells may transform to generate oncogenic stem cells that drive pediatric renal cancer. We have shown by genetic-lineage tracing that follows clonal evolution of single kidney cells that once nephrons are generated, cell replacement and cell growth is driven by fate-restricted uni-potential clonal expansions in varying kidney segments arguing against a multipotent adult stem cell model. We term this lineage-restricted progenitor characteristics. Lineage-restriction is similarly maintained during ex-vivo human kidney growth and in murine kidney organoids grown in culture.

Finding ways to ex vivo preserve and expand the observed in vivo kidney-forming capacity inherent to both the fetal and adult kidneys is crucial for taking renal regenerative medicine forward. Some of the strategies that we are using to achieve this are sorting human embryonic nephron stem/progenitor cells, growing adult kidney spheroids/organoids or reprogramming differentiated kidney cells towards expandable renal precursors. We further demonstrate beneficial functional effects of human nephron-forming progenitor cells in mouse models of acute and progressive kidney injury both by differentiation-dependent and paracrine mechanisms.

The ability to promote kidney tissue restoration may be relevant in patients with kidney disease and transform renal medicine.