BIOGRAPHICAL SKETCH

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NAME: Yi Xu

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

POSITION TITLE: Assistant Professor

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 YEARS	FIELD OF STUDY
Shanghai Jiao Tong University, School of Medicine	M.D.	1996	Clinical Medicine
	ECFMG	2018	#07808116 for USMLE
Kyoto University, School of Medicine, Kyoto, Japan	Ph.D.	2005	Neurobiology & Anatomy
Dana Farber Cancer Institute, Boston, MA	Fellowship	2012	Neurobiology & Cancer Biology
Children's Hospital, Boston, MA	Fellowship	2013	Neurobiology
Loma Linda University, Loma Linda, CA	Research Specialist	2018	Immune regulation AML, IBD, PTOA, AD

A. Person Statement

My current studies are focused on to evaluating the therapeutic effect of tumor infiltrating lymphocyte (TIL) based adoptive cell therapy in combination with PD-1 inhibitors and 5-Azacytidine (AZA) to treat AML and prevent relapse. Recently, combination immunotherapies have been proposed to enhance treatment efficacy of PD-1/PD-L1 blockades in treating gastrointestinal malignancies. Adding chemotherapies to PD-1/PD-L1 inhibitors can not only sensitize tumors to respond to immunotherapies, but also increase CD8+ T cell infiltration and cytotoxicity to tumors in preclinical studies. We hypothesize that combination immunotherapy of *ex vivo* expanded autologous PD-1-inhibited-TILs and AZA will produce a superior anti-leukemic therapeutic effect by reducing the survival of LSCs and AML blasts *ex vivo* and extending the overall survival of AML patient derived xenograft (PDX) mice. These studies are consistent with my research interests over the past 15 years to take advantage of cutting-edge technologies to develop effective therapeutic approaches for human diseases.

B. Positions and Employment

California

2019- Assistant Professor, Department of Medicine, Loma Linda University, Loma Linda, CA
2014-2018 Research Specialist, Division of Regeneration Medicine, Department of Medicine, LLU

Boston

2012-2013 Research Fellow; Children's Hospital (Boston), MA
2005-2012 Research Fellow; Dana Farber Cancer Institute, Harvard Medical School, Boston, MA

Other Experience and Professional Memberships

2004- Member, Society of Neuroscience (USA)
2003- Member, Society of Neuroscience (Japan)
2003- Member, International Society for Stem Cell Research

Honors
2001-04 Pre-doctoral Fellowship, Graduate School of Medicine, Kyoto University, Japan
2002 Travel Grant Award for the Asian Stem cell Research Conference, Australia

C. Contribution to Science

1) One part of my lab research interests is looking for appropriate therapeutic approaches to treat AML and prevent relapse through the earlier detection of relapses, inhibition of malignant expansion of leukemia stem cells, and enhancement of bone marrow regeneration.

$1,25(OH)_2D_3$, the active form of vitamin D, has been well known to have dynamic functions including immune regulation, neuron protection, repair of gut epithelial barrier, and bone health. Accumulating evidence in cancer research has shown inhibitory effects of vitamin D and its analogs on the proliferation of cancer cells, suggesting $1,25(OH)_2D_3$ as a potential preventive/therapeutic agent against cancer stem cells (CSCs).
To facilitate the translational studies, we have been designing strategies that can deliver the $1,25(OH)_2D_3$ specifically into the immune system such as bone marrow. I have been working on several projects including genetically modified adoptive cell therapies and immunotherapies for the treatment of AML.

- **Patent: Gene therapy for AML using hematopoietic stem cells** Provisional Patent with Loma Linda University, (Attorney Docket No.: 101578-1074418-003500PR)
  Peer-reviewed Publications:
  A Novel Vitamin D Gene Therapy for AML
- **Xu Y**, Guido Marcucci, David Chi, Justin Lyu, Jeffrey Xiao, Linh Hoang Gia Pham, Kimberly Payne, David Jeston Baylink, Mark Reeves, Huynh Cao, **(A new gene therapy for AML, and the manuscript will be submitted in 2019.)**
- Huynh Cao*, **Xu Y***, de Necochea-Campion R, David J. Baylink, et al. Vitamin D and analogue's application in AML treatment. ***Experimental Hematology*** 50: 1-12, (2017) **PubMed PMID: 28174131**
- Chih-Huang Li, Xl Tang, Wasnik S, Wang Xh, Zhang JT, **Xu Y**, et al. Mechanistic Study of the Cause of Decreased Blood 1,25-Dihydroxyvitamin D in Sepsis. ***BMC Infectious Disease* (*In Press*, 2019)**

2) One part of my lab research interests is to contribute to the understanding of $1,25(OH)_2D_3$'s biological functions in immune regulation and tissue regeneration in autoimmune diseases like Inflammatory Bowel Disease (IBD), Experimental Autoimmune Encephalomyelitis (EAE), and their potentials in the prevention of bone loss and fracture healing through the modulation of bone marrow stem cells.

Peer-reviewed Publications:

- **Xu Y,** Yanmei Cheng, David J. Baylink, et al. CYP27B1 Adoptive Cell Therapy Ameliorates TNBS-induced Mouse IBD Model through Colonic Stem Cell Regeneration **(To be submitted, 2019)**
- **Xu Y***, Yanmei Cheng*, Christian Chan, et al. In Vivo Generation of Gut-Homing Regulatory T Cells for the Suppression of Colitis. ***Journal of Immunology***, 202 (12):3447-3457 (2019) **PubMed PMID: 31053627**
- **Xu Y***, Samiksha Wasnik*, David J Baylink, et al. Overlapping Peptide Library to Map Qa-1 Epitopes in a Protein ***Journal of Visualized Experiments*** Dec.20, 130, (2017) **PubMed PMID: 29286392**
- Wasnik S, Lakhan R, Baylink DJ, Rundle CH, **Xu Y**, Zhang J, et al. Cyclooxygenase 2 augments osteoblastic but suppresses chondrocytic differentiation of $CD90_+$skeletal stem cells in fracture sites. ***Science Advances*** Jul 31, 5(7), (2019) **PubMed PMID: 31392271**

3) My postdoc research in Boston contributed to the understanding of dorsal spinal cord neurons' development, development of ascending pathways between spinal cord and brain and neural circuitry of pain:
Fundamental questions including genetic and molecular mechanisms underlying the neural circuitry between spinal cord and brain have been remained to be answered. The dorsal horn of the spinal cord is a major component of the somatosensory circuitry. As a preliminary integration center, it processes and transmits somatic sensory information like pain, heat and cold to the higher brain center. In my previous 3 first author papers in the Journal of Neuroscience, I utilized genetic methods to classify the dorsal horn neurons during the developmental stages by revealing the neuropeptides' expression in laminar-specificity patterns. In addition, I made a new TLX3 conditional Cre-LoxP knockout mouse line and demonstrated a new peptide-modulated pain circuitry in adult dorsal spinal cord bypassing the lethal problem of conventional TLX3 KO problem. Previous knowledge of long-range ascending projection neurons was mostly based on the morphological analyses. My genetic studies revealed that neuropeptides can be used as alternative molecular biomarkers to classify those special projection neurons, which have dynamic sensory modalities. My other results demonstrated that Tlx3 is

required for the correct development of spino-thalamic ascending pathways, a neural circuitry between spinal cord and thalamus **(novel but not published yet)** (saw a familiar idea paper from the previous lab in Nature, 2019). My continuous work will look for the method of reconstructing the somatosensory relay pathways between spinal cord and brain in stroke, spinal cord injury and cancer pre-clinical models.

Peer-reviewed Publications:

- **Xu Y***, Lopes C*, Wende H, Guo Z, et al. Ontogeny of excitatory spinal neurons processing distinct somatic sensory modalities. ***Journal of Neuroscience*** Sep 11; 33(37):14738-48. (2013) **PubMed PMID: 24027274**
- **Xu Y**, Lopes C, Qian Y, Liu Y, Cheng L, et al. Tlx1 and Tlx3 coordinate specification of dorsal horn pain-modulatory peptidergic neurons. ***Journal of Neuroscience*** Apr 9; 28(15):4037-46. (2008) **PubMed PMID: 18400903**
- Lopes C*, Liu Z*, **Xu Y***, Ma Q. Tlx3 and Runx1 act in combination to coordinate the development of a cohort of nociceptors, thermoceptors, and pruriceptors. ***Journal of Neuroscience*** Jul 11; 32(28):9706-15. (2012) **PubMed PMID: 22787056**
- Ross SE, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu L, Mok SI, Shah A, Savner EM, Tolias C, Corfas R, Chen S, Inquimbert P, **Xu Y**, McInnes RR, Rice FL, Corfas G, Ma Q, Woolf CJ, Greenberg ME. Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. ***Neuron***. Mar 25; 65(6):886-98. (2010) **PubMed PMID: 20346763**

4) My PhD research training contributed to Neuroscience field by the discovery of Neurogenesis in Adult Mammalian Hypothalamus, and Tanycytes are the neural stem cells in adult hypothalamus. Also my work revealed endogenous stem cell therapy could be utilized to treat spinal cord injury and brain diseases:
There is no effective treatment for spinal cord injury (SCI). Improved emergency care for people with spinal cord injuries and aggressive treatment and rehabilitation may minimize damage to the nervous system, however most SCI causes permanent disability, especially loss of movement (paralysis) and sensation below the site of the injury, which makes a huge challenge for both medical-care providers and families. For the regeneration field, more and more researchers believe that stem cell therapy may give doctors and patients hope that repairing injured spinal cords is a reachable goal. Stem cell therapy is the replacement of diseased, dysfunctional or injured cells with for example embryonic stem cells, which has raised significant ethical questions because embryonic stem cells are obtained from destroyed early-stage embryos. To avoid the ethic problem, I have successfully isolated viable neural stem cells from the postmortem rodent brains, suggesting that postmortem neural stem cells could potentially become an acceptable alternative cellular resource instead of highly controversial embryonic stem cells. More importantly, after transplanted into the injured spinal cord, these neural stem cells were found to survive in the injured tissues and differentiate into neural cells which were integrated into local tissues and helped regeneration. Further to look for other new therapies for the SCI, I found that many normally quiescent neural stem cells proliferate broadly after SCI. My results revealed that endogenous neural stem cells could be utilized to replace the injury-damaged tissues, and facilitate the preservation of intact tissues, suggesting a new direction of treatment of SCI.

Peer-reviewed Publications:

I discovered neural stem cells and neurogenesis in adult mammalian hypothalamus, **the hormone center**. My paper provided the first evidence that tanycytes along the 3rd ventricle wall of the adult hypothalamus are neural stem cells, persisting to generate functional neurons in the adulthood.

- **Xu Y$**, Tamamaki N, Noda T, Kimura K, Itokazu Y, et al. Neurogenesis in the ependymal layer of the adult rat 3rd ventricle. ***Experimental Neurology*** Apr192 (2):251-64.(2005).**This paper was selected as the Cover Story of that issue and has been cited by many papers studying neurogenesis and neural stem cells in the adult hypothalamus. $: corresponding author; PubMed PMID: 15755543**
- **Xu Y$**, Kimura K, Matsumoto N, Ide C. Isolation of neural stem cells from the forebrain of deceased early postnatal and adult rats with protracted post-mortem intervals. ***Journal of Neuroscience Research***. Nov 15; 74(4):533-40. (2003).**This paper was selected as the Cover Story of that issue. $: corresponding author; PubMed PMID: 14598297**
- **Xu Y$**, Kitada M, Yamaguchi M, Dezawa M, Ide C. Increase in bFGF-responsive neural progenitor population following contusion injury of the adult rodent spinal cord. ***Neuroscience Letter***. Apr 24; 397 (3):174-9. (2006) **$: corresponding author; PubMed PMID: 16406666**
- Cheng L, Samad OA, **Xu Y**, Mizuguchi R, Luo P, et al. Lbx1 and Tlx3 are opposing switches in determining GABAergic versus glutamatergic transmitter phenotypes. ***Nature Neuroscience*** Nov; 8(11):1510-5. (2005) **PubMed PMID: 16234809**

D. Research Support

Ongoing Research Support

- Research Innovation Grant (Cao):

Department of Medicine, Loma Linda University.Gene therapy for AML.
Role: Co-Investigator. 4/2019-3/2021. Percentage effort: 50%. Percentage experimental results:100%

Completed Research Support

- Discovery Inception Award, CIRM 2018 (Cao):

California Institute for Regenerative Medicine. Gene therapy for AML using hematopoietic stem cells.
Role: Co-Investigator. 4/2018-3/2019. Percentage effort: 80%. Percentage experimental results:100%

- Young Investigator Award, ASCO 2017 (Cao):

Gene therapy for AML using hematopoietic stem cells.
Role: Co-Investigator. 7/2017-6/2018. Percentage effort: 50%. Percentage experimental results:100%

- Research Innovation Grant (Tang):

Department of Medicine, Loma Linda University. Immunotherapy for Inflammatory Bowel Disease.
Role: Co-Investigator. 4/2015-6/2017. Percentage effort: 50%. Percentage experimental results:100%

- R01NS047710 (NIH/NINDs):

Molecular control of spinal relay sensory neuron phenotypes and pain behaviors.
Role: 2005-12 Postdoctoral Investigator (I did all experiments including generate a new transgenic mouse line-Tlx3-conditional knockout and contributed many new ideas & evidences of ascending neural circuitry to the lab which helped renew the grant.), DFCI/ Harvard Medical School. Percentage effort: 100%. Percentage experimental results:100%