APPLICANT'S BIOGRAPHICAL SKETCH

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BIOGRAPHICAL SKETCH

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NAME: Huynh Cao

eRA COMMONS USER NAME (credential, e.g., agency login): hcao01

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 MM/YYYY	FIELD OF STUDY
University of California, Los Angeles	B.S.	06/2003	Biochemistry
University of California, Los Angeles, David Geffen School of Medicine	M.D.	6/2008	Medicine
Harbor-UCLA Medical Center Torrance, CA	Internship	6/2009	Surgery
Albany Medical Center Albany, NY	Residency	6/2011	Surgery
St. Mary's Medical Center San Francisco, CA	Residency	6/2014	Internal Medicine
Loma Linda University Medical Center Loma Linda, CA	Fellowship	6/2014-6/2017	Hematology & Oncology fellowship

A. Personal Statement

Throughout my undergraduate study as well as professional career, I have worked in multiple labs as a research assistant and have involved in several clinical trials as a co-Investigator and Principal Investigator. I have developed a special interest in hematology field, specifically leukemia. During my second year of fellowship at Loma Linda University Medical Center, I was awarded a research grant from the Department of Medicine for my *in vitro* work in AML cells differentiation using mesenchymal progenitor cells with ectopically expressed CYP27B1 gene. This preliminary data is the basis for my supporting grants from ASCO Conquer Cancer Foundation, California Institute for Regenerative Medicine (CIRM) and Research Innovation Grant from Loma Linda University.

My personal goal is to help patients with acute leukemia, who are going through treatment experience less suffering. Current treatment for AML requires intensive chemotherapy to achieve complete remission, a process highly toxic to unfit or older patients. Thus, better-tolerated and less toxic treatment options are urgently needed. Groundbreaking discovery such as differentiation therapy has shown extraordinary success in treating acute promyelocytic leukemia (APL), a subtype of AML, with retinoic acid (a vitamin A metabolite) and arsenic trioxide. In this era, APL can be cured without using cytotoxic chemotherapy. Development of a clinically applicable differentiation therapy for more subtypes of AML will help provide a less toxic treatment alternative to many more patients.

B. Positions and Honors

Positions

2014-2017 Hematology & Oncology Fellow, Loma Linda University Medical Center, Loma Linda, CA
2017-current Assistant Professor at Loma Linda University Medical Center, Loma Linda, CA

Honors and Awards

1999 Award from American Chemical Society in Chemistry
2002 Summer Research Award, UCLA Department of Biochemistry
2003 Departmental Highest Honor, Summa Cum Laude in Biochemistry
2005 Research Award, UCLA School of Medicine Short Term Research Training Program
2013-2014 Chief Medical Resident, St. Mary's Medical Center, San Francisco
2016 Loma Linda University Medical Center (LLUMC), Department of Medicine Research Award
2017 ASCO Conquer Cancer Foundation Young Investigator Award
2018 CIRM Inception Grant
2018 ASCO Travel Grant for Scientific and Career Development Retreat
2018 ASCO Virtual Mentors Program
2018 HemOnc Today Next Gen Innovators
2019 Research Innovation Grant from Loma Linda University

Other Experience and Professional Memberships

2011-current Member, American College of Physicians
2013-2014 Member, American Society of Hospital Medicine
2013-2014 Member, Northern California Melanoma Center Research Team
2013-current Member, American Society of Clinical Oncology
2014-current Member, American Society of Hematology

C. Contribution to Science

1. CYP27B1 gene therapy in combination with chemotherapy for acute myeloid leukemia.
Induction chemotherapy with cytotoxic agents remains the initial standard of care for acute myeloid leukemia (AML). The current treatment strategy is exceedingly toxic for older adult patients who frequently present with multiple co-morbidities. Active vitamin D3 (1,25-(OH)2-D3) has shown promising preclinical success in vitro. The concentrations of active VD3 required to effectively induce differentiation (70-80% of blast cells) in vitro are typically in the range of 100-1000 nanomolar (nM); however, a serum level of such concentration would certainly result in hypercalcemia in humans (the normal concentration of active VD3 is around 0.1 nM in humans). To overcome this limitation, we used genetically engineered MOLM-14 AML cells (designated as CYP27B1-GFP-MOLM14) as vehicle cells to deliver the VD3 activating enzyme (CYP27B1, 1-a-hydroxylase-25-OH-VD3) to the bone marrow where endogenous inactive VD3 will be converted to active VD3. We used this gene therapy in combination with low dose 5-Azacytidine (AZA) in human leukemic xenograft mice. The AZA + CYP-GFP-MOLM14 group exhibited longer overall survival compared to the control group (GFP-MOLM14 only) (13.8 days vs. 8.6 days, $p = 0.05$), and the AZA + GFP-MOLM14 group (13.8 days vs. 11.2 days, $p = 0.05$).

Cao, H, Xu Y, Necochea-Campion R, Baylink D, Payne KJ, Tang X, Ratanatharathorn C, Ji Y, Mirshahidi S, Chen CS. Application of vitamin D and vitamin D analogs in acute myelogenous leukemia. Exp Hematol 50: 1-12 (2017).
Cao H, Xu Y, Payne KJ, Necochea-Campion R, Chen CS, Baylink D, Tang X, Marcucci G. CYP27B1 gene therapy for acute myeloid leukemia. Presented abstract at the ASCO Scientific and Career Development Retreat 2018. Manuscript in preparation. To be submitted to Leukemia. November 2019.

2. Vitamin D's biological functions in immune regulation and tissue regeneration, and their potentials in the prevention of malignant formation of cancer stem cells.

Accumulating evidence has shown inhibitory effects of vitamin D and its analogs on the cancer stem cell signaling pathways, suggesting vitamin D as a potential preventive/therapeutic agent against cancer stem cells (CSCs). Preclinical studies in animals appear to support calcitriol, the active form of vitamin D, as a drug for managing a variety of tumors, by its well-known inducer function of the terminal differentiation such as myeloid leukemia cells into monocytes and macrophages. Also calcitriol has other different functions including immune regulation, neuron protection, repair of gut epithelial barrier, and bone health. To facilitate the translational studies, we have been designing strategies that can deliver the calcitriol specifically into the immune system like bone marrow, the gut, and the brain. To fulfill this goal, I have been working on the projects of tissue-specific targeting and calcitriol's role in Regulatory T cell's generation and transgene cell therapy for the AML, experimental colitis [an animal disease that is a well-established model for human inflammatory bowel disease (IBD)] for the past two years. I am currently writing two papers about the novel therapies for IBD. The goal is to further our understanding of calcitriol's role in the immune regulation, inhibition of cancer stem cells' generation and differentiation of immature stem cells like AML blasts, and tissue regeneration. In addition, we are seeking potential clinical applications of our innovative strategies.

Xu Y, Cheng Y, **Cao H,** Chan C, Chelliah H, Li CH, Wang X, Lau W, Baylink D, Qin X, Tang X. *In vivo* generation of gut-homing regulatory T cells for the suppression of colitis. (Submitted to Journal of Immunology, conditionally accepted). May 2019.
Xu Y, **Cao H,*** Cheng Y, Baylink D, Goel G, Xiaolei Tang. CYP27B1 Adoptive Cell Therapy Ameliorates TNBS-induced Mouse IBD Model through modulation of colon stem cells (to be submitted Journal of Clinical Investigation). 2019. *Co-first author.

3. Biological effects of anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody formation. GM-CSF is a hematopoietic growth factor, which stimulates proliferation and differentiation of hematopoietic progenitor cells. In a single arm study, we investigated the development of binding and neutralizing antibodies to GM-CSF in patients receiving prolonged therapy with GM-CSF as adjuvant therapy for melanoma. We found that 93% of 43 patients developed binding antibodies and 42% developed both binding and neutralizing antibodies. In those with neutralizing antibodies, we observed a diminution of the biological effects of GM-CSF (increase in white blood cell count, percent eosinophils, or neopterin levels). We concluded that the development of neutralizing antibodies to GM-CSF might abrogate the potential benefit of this adjuvant treatment for melanoma.

Spitler LE, **Cao H**, Piironen T, Whiteside TL, Weber RW, Cruickshank S. Biological effects of anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody formation in patients treated with GM-CSF (sargramostim) as adjuvant therapy of melanoma. Am J Clin Oncol 40(2): 207-213 (2017).

4. Novel ELISA assay to detect peripheral blood exosomes for monitoring for AML disease recurrence. In collaboration with Dr. Mitsuhashi from NanoSomiX, we developed a novel sandwich enzyme-linked immunosorbent assay (ELISA) by using a combination of monoclonal antibodies against 2 different leukocyte antigens. Since CD81 is one of established surface markers of exosomes, $CD117^+$ $CD81^+$ double positive ELISA signals indicate the presence of $CD117^+$ exosomes and its quantity in the plasma. Since plasma does not contain any cells, such double positive signals are considered to be derived from exosomes. We used this assay to test plasma samples of 6 AML patients before and after chemotherapy induction. The exosomes quantities correlated with the disease status in the bone marrow.

Cao H, Xu Y, Marcucci G, Payne K, Baylink D, Chen CS, Mitsuhashi M. Novel marker sandwich immunoassay for the detection of precursor- and mature granulocyte-derived exosomes in peripheral blood. Manuscript in preparation.

5. Participation in Clinical Trials. I have been involved in multiple clinical trials as Co-Investigators or PI since I was an internal medicine resident at St. Mary's Medical Center in San Francisco. I helped the PI, Dr. Lynn Spitler, screen and enroll many patients to the melanoma clinical trials. I also acted as the

contact person between the Northern California Melanoma Center and the UCSF Melanoma Center. At LLUMC Cancer Center, I have participated in many phase 2 and 3 clinical trials; most recent is the SWOG S1318 protocol, which evaluates the effectiveness of Blinatumomab for older patients (greater than 65 years of age) with newly diagnosed Philadelphia-Chromosome negative acute lymphoblastic leukemia. I truly believe that being able to participate in these clinical trials will make me a better and complete doctor. They will not only help me familiarize with the trial's design and process but also help strengthen my clinical knowledge.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PIYddBZdmoAE/bibliography/50714238/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

Loma Linda University Medical Center (LLUMC) 4/1/2019 - 3/30/2023
Sponsor: Department of Medicine; Research Innovation Grant
Project Title: Mechanism of action of combination therapy of chemotherapy and gene therapy on AML
Goal: To study mechanism of action of active VD3 and different types of chemotherapy on AML pathways with a specific focus on FLT3 mutation.
Role: PI Mentor: Dr. Marcucci, Dr. Payne.

Completed Research Support

LLUMC 1/1/2017 - 6/30/2017
Sponsor: Department of Medicine
Project Title: Application of CYP27B1 gene and vitamin D in *in vitro* setting for acute myelogenous leukemia
Goal: To study the efficacy of novel cell therapy for acute myelogenous leukemia in an *in vitro* setting.
Role: Co-PI Mentor: Dr. CS Chen

American Society of Clinical Oncology (ASCO) 7/1/2017 - 6/30/2018
Sponsor: ASCO Young Investigator Award 2017; Conquer Cancer Foundation
Project Title: Gene transduced mesenchymal progenitor cell for Vitamin D delivery in acute myeloid leukemia
Goal: To study the efficacy of novel cell therapy for acute myeloid leukemia in an in vivo setting
Role: PI Mentors: Dr. Baylink, Dr. Payne, Dr. CS Chen

California Institute for Regenerative Medicine (CIRM) 3/01/2018 - 3/31/2019
Sponsor: CIRM; Discovery Inception Award
Project Title: Bone Marrow Targeting of Hematopoietic Stem Cells (HSCs) Engineered to Overexpress 25-OH-D3 1-α-hydroxylase for Acute Myeloid Leukemia Therapy
Goal: To engineer HSCs to overexpress 25-OH-D3 1-α-hydroxylase and optimize homing of engineered HSCs to the bone marrow.
Role: Co-PI PI: Dr. David Baylink