COHA Translational Fellowship Opportunity for Residency-Trained Veterinary Specialists

Molecular targeting of resistant canine diffuse large B cell lymphoma

Area of Research: Our studies involve the collaborative and synergistic efforts of basic and clinical researchers with expertise in canine and human oncology, hematology, and genome science. It will provide unique training opportunity for a medical oncology fellow.

University and Department:
Medical Sciences Department
University of Wisconsin-Madison

Primary Mentor:
Xuan Pan, VMD, PhD, DACVIM (Oncology)
Associate Professor
Medical Sciences Department
University of Wisconsin-Madison
Email: xuan.pan@wisc.edu

Mentor Team:
Emery H. Bresnick, PhD
Gary Felsenfeld Professor of Cell and Regenerative Biology
Director, Wisconsin Blood Cancer Research Institute
Co-Director, Genetic and Epigenetic Mechanisms Program, Carbone Cancer Center
University of Wisconsin School of Medicine and Public Health
Wisconsin Institutes for Medical Research
Email: ehbresni@wisc.edu

Lixin Rui, PhD
Associate Professor
Department of Medicine
University of Wisconsin
School of Medicine & Public Health
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Description of Potential Research Project(s):
Diffuse large B cell lymphoma (DLBCL) is one of the most common hematological cancers in humans and dogs. The current standard of care for human DLBCL (hDLBCL) and canine DLBCL (cDLBCL) involves cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). However, almost all of canine responders will relapse within one year of the CHOP treatment. Because of the high frequency of relapse and comparable attributes to hDLBCL, cDLBCL offers a powerful comparative model to assess drug resistance mechanisms and develop novel therapeutic strategies to surmount unmet clinical needs. The evolution of multiple tumor subclones during tumor progression generates intratumoral heterogeneity, which plays a role in intrinsic and acquired treatment resistance. Molecular insights into the difference in clinical outcomes of individual patient and the resistance mechanism of CHOP treatment remain largely unknown. We hypothesize that certain genetic mutations confer advantages in lymphoma cell growth, resulting in clonal expansion of the affected cells after CHOP treatment. The project aims to establish tumor-intrinsic and -extrinsic mechanisms that determine CHOP treatment resistance. By integrated analyses of single-cell RNA-seq and whole exome sequencing data, our studies will determine changes in the gene expression profile and mutations in different populations of cells and identify drug-resistance accumulating mutations and pathways. Our study will shed new cellular and molecular insights into the mechanism of CHOP resistance, which provide the mechanistic rationale for the development of targeted therapeutic strategies in both human and canine DLBCLs.

Additional Training Opportunities:

The mentoring team involves the collaborative and synergistic efforts of basic and clinical researchers with expertise in canine oncology, human oncology, lymphomagenesis, and genome science. Given Dr. Pan’s expertise in clinical/translational research using in vitro and in vivo tumor models, Dr. Bresnick’s expertise in genome science and hematology, and Dr. Rui’s expertise in cancer genomics and biology, the collective efforts of the investigators generate a uniquely qualified team to position to train a successful independent researcher in the field of comparative oncology.

Checklist of Scientific and Career Milestones to be Achieved During the Award

- Meet biannually with mentoring committee to evaluate research progress
- Attend weekly Carbone Cancer Center Grand Rounds
- Attend monthly UW Blood Research seminar
- Attend ICTR Scientific Writing Workshop.
- Present at UW Blood Research Program (05-23).
- Present at the ASH Annual meeting (12-23)
- Attend “Advanced Short Course for Clinical and Translational Research” provided by UW ICTR.
- Attend and present at the Veterinary Cancer Society Annual meeting (10-23).
- Attend "Qualitative and Mixed Research Education Resources" provided by UW ICTR
- Attend “Research Ethics and Professional development” course
- Collaborate with advisory committee to submit proposal for Companion Animal Fund.
BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors. Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: PAN, XUAN

eRA COMMONS USER NAME (credential, e.g., agency login): xpan24

POSITION TITLE: Associate 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.)

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<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>END DATE MM/YYYY</th>
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<tr>
<td>Nanjing University of Aeronautics and Astronautics, Nanjing, P. R. China</td>
<td>BA</td>
<td>07/1998</td>
<td>English</td>
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<tr>
<td>Iowa State University, Ames, IA</td>
<td>-</td>
<td>05/2002</td>
<td>Veterinary Medicine</td>
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<td>PhD</td>
<td>08/2010</td>
<td>Cell &amp; Molecular Biology</td>
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<td>Intern</td>
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<tr>
<td>University of Wisconsin, Madison, WI</td>
<td>Resident</td>
<td>07/2013</td>
<td>Veterinary Oncology</td>
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A. Personal Statement

As a veterinary research scientist, I am uniquely positioned to leverage my expertise and skills to advance basic research on hematopoiesis and to develop novel efficacious treatments for hematopoietic diseases, including cancers of the hematopoietic system in humans and animal species. Early in my training, I developed a strong interest in hematopoiesis and an awareness of the burden and prevalence of hematopoietic/hematological disorders in humans and other animal species. Later, when I became aware of the power and importance of stem cell research for understanding hematopoiesis, I became especially interested in the genetic and epigenetic regulation of hematopoietic stem cell (HSC) differentiation. I am highly motivated to discover how stem cell technology can be used to improve cancer treatment modalities and patient outcomes. Since early in my career, my goal has been to carry out cutting-edge research that has significant translational impact in this important research area. Being a veterinary oncologist, I have implemented translational-based research focusing on developing novel targeted therapy by utilizing a naturally occurring hematologic cancer model in pet dogs. In August 2017, I received the national American Veterinary Medical Association/American Veterinary Medical Foundation Young Investigator Award. Both of my basic science and clinical science studies are well supported by NIH R01 and private funding. I have mentored over 40 graduate students, postdocs, residents, interns and undergraduate students. My clinical expertise in veterinary oncology and extensive experience of mentoring will ensure the successful completion of COHA translational fellowship.


B. Positions, Scientific Appointments and Honors

Positions and Employment
- 2013 –2020: Assistant Professor, University of Wisconsin-Madison, Madison, WI
- 2020-: Associate Professor, University of Wisconsin-Madison, Madison, WI

Other Experience and Professional Memberships
- 2008 -: Member, American Veterinary Medical Association
- 2011 -: Member, Veterinary Cancer Society
- 2014 -: Member, American College of Veterinary Internal Medicine (DACVIM-Oncology)
- 2014 -: Committee, Clinical Translational Science Award (CTSA) One Health Alliance
- 2015 -: Member, American Society of Hematology
- 2015 -: Member, International Society for Experimental Hematology (ISEH)
- 2020: American Society of Hematology (ASH) Abstract Review Committee
- 2020: 62nd ASH Annual Meeting Moderator
- 2021 -: Associate editor of Journal of Veterinary Internal Medicine

Honors
- 2001: Academic Scholarship, Iowa State University
- 2003 - 2004: Dean’s List, University of Pennsylvania
- 2004: J. Maxwell Moran, Sr. Dean’s Scholarship, University of Pennsylvania
- 2004: Phi Zeta Honor, University of Pennsylvania
- 2004: Veterinary Student Research Award, University of Pennsylvania
- 2007: Phi Zeta Honor, University of Pennsylvania
- 2007: Veterinary Student Research Award, University of Pennsylvania
- 2017: Young Investigator Award, American Veterinary Medical Association/American Veterinary Medical Foundation

C. Contribution to Science

1. Polycomb Group Protein network in B cell development

My dissertation research project in Dr. Michael Atchison’s laboratory focused on the epigenetic regulation of B cell development. I successfully identified a critical epigenetic regulator that orchestrates the Polycomb Group (PcG) protein network in B cell development. YY1 is a multifunctional PcG protein that binds to multiple enhancer binding sites in immunoglobulin (Ig) loci and plays vital roles in early B
cell development. Conditional knock-out of YY1 results in cell cycle arrest in pro-B cells, reduced Ig locus contraction and suppression of distal variable gene rearrangement. The mechanisms that control YY1 functions in VDJ rearrangement and Ig locus contraction were largely unknown. My studies showed that YY1 PcG function is required for Ig kappa rearrangement. YY1, EZH2 and condensin proteins co-localize at numerous sites across the Ig kappa locus. Knock-down of a condensin subunit protein or YY1 reduced rearrangement of Ig kappa genes, suggesting a direct role for YY1-condensin complexes in Ig kappa locus structure and rearrangement. My findings provide specific molecular details to key functions that regulate B-cell development and for the first time implicate condensin complex proteins in Ig rearrangement. I was appointed to an NIH T32 Training Grant for studies in genetics, cancer biology, and comparative medicine during my dissertation phase.


2. Molecular Determinants for YY1 Control of Hematopoietic Stem Cell Development

To fully understand hematopoietic cancer, we must first refine our understanding of normal hematopoiesis. In this manner, the success of our basic research studies directly influences the success of our translational studies. It is now well known that hematopoietic Stem Cells (HSCs) are undifferentiated, self-renewing, pluripotent cells that have the capacity to differentiate into all mature lineage-specific cells in adult blood. If the correct balance between HSC self-renewal and differentiation is not maintained, hematopoietic cancers such as leukemia and lymphoma can develop. Early work by my group, supported by an NIH K01 award, demonstrated that a conditional knockout of Yy1 in HSCs decreased HSC long-term repopulating activity, while ectopic expression of YY1 expanded HSCs. Although the YY1 PcG domain is required for Igk chain rearrangement in B cells, the YY1 mutant lacking the PcG domain retained the capacity to stimulate HSC self-renewal. YY1 deficiency deregulated the genetic network governing HSC cell proliferation, impaired stem cell factor/c-Kit signaling, and disrupted mechanisms that confer HSC quiescence. These results reveal how YY1, a ubiquitously-expressed transcriptional repressor, mediates lineage-specific functions to control adult hematopoiesis. Furthermore, we showed that while YY1 mediated PcG function is required for both B and T cell development, it is not required in the myeloid lineage, providing specific molecular details and insight into the epigenetic landscape in lymphocyte development. These studies provided the foundational basis for our R03 and R01 awards. Our current studies focus on YY1-dependent effects on chromatin accessibility, higher-order
chromatin/chromosome structure and activation/repression of target genes including *Kit* and *Smc3*.


3. Novel targeted therapy for treating diffuse large B cell lymphoma

Naturally-occurring cancers in pet dogs share many similarities to human cancers including histological appearance, molecular target, tumor genetics, biological behavior and response to therapeutics. The lack of conventional therapies with sustainable efficacy for diffuse large B cell lymphoma (DLBCL) in humans and dogs is strong motivation for additional research on novel therapeutic approaches for DLBCL. My studies showed that the STAT3 pathway is upregulated in canine DLBCL and JAK1/2 inhibitors suppress canine lymphoma cell growth. I designed and conducted a phase I clinical trial in canine cancer patients, and defined the maximum tolerated dose and dose-limiting toxicity of a novel targeted drug combination-therapy using a receptor tyrosine kinase inhibitor plus cytotoxic chemotherapy. My findings justify further clinical investigation of the safety and efficacy of JAK1/2 inhibitors in canine DLBCL and suggest new opportunities for novel anticancer therapies in dogs and humans. The study was funded by a Pfizer Animal Health Grant and Veterinary Cancer Society, and led into a Late-Breaking presentation at American College of Veterinary Internal Medicine Annual Forum (2016) and a state-of-the-art presentation at Veterinary Cancer Society Annual Conference (2017). I served as the primary investigator and resident mentor on these studies. Our current studies focus on determining the distinct molecular profile of tumor intrinsic and microenvironmental factors that contribute to chemotherapy resistance in canine DLBCL, and developing a combinatorial treatment regimen by targeting JAK/STAT and NF-κB signaling for refractory/relapsed DLBCL.


c. Lu Z, Hong CC, Jark PC, Assumpção ALFV, Bollig N, Kong G, **Pan X**. JAK1/2 Inhibitors AZD1480 and CYT387 Inhibit Canine B-Cell Lymphoma Growth by
