UC Davis Comparative Oncology Program and Current Research

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Professor Radiation Oncology
Director, Center for Companion Animal Health
Co-Program Leader Comparative Oncology Program
My Background
The mission of the Center for Companion Animal Health is to provide research and program support to improve the health and well-being of companion animals. We accomplish this mission through:

- Raising funds
- Supporting animal health studies
- Providing facilities
- Serving as an educational resource
- Developing programs related to animal health

Oncology Core, Genetics, Mammalian ecology and conservation, immunology and Cardiology Laboratories
CCAH - History

- Founded in 1991
  - Companion Animal Laboratory Fund (1973)
  - Comparative Cancer Center (1987)
- Faculty Support - >$16,000,000
- Facility Construction - ~$17,000,000
- Resident Project Support >$1,100,000
CCAH – Pilot Research Grants

**FACULTY – 15K**

- Fund one yearly call and occasional off-cycle grants
- Reviewed by scientific advisory committee
- Provide funds for 1-yr research projects
- Provide seed money to generate preliminary data for extramural funding

**RESIDENT – 5K**

- 3 calls per year
- Reviewed by scientific advisory committee
- Now funded through recent endowment earnings for this purpose

Matching Funds Grants, Equipment Grants & Publication Costs
CAAH Funded Cancer Grants

- Differential role of sonic hedgehog transcription factors Gli1 and Gli2 in canine osteosarcoma

- Potency and stability of compounded chemotherapy drugs

- Effects of fasting on the incidence of delayed-type chemotherapy induced nausea and vomiting in dogs receiving doxorubicin
Veterinary Center for Clinical Trials
Veterinary Medical Teaching Hospital

- Largest veterinary teaching hospital in the world
- >50,000 animal patients seen each year
- Largest clinical training program in the word
  - 145 DVM students/year, ~100 residents, 7 interns, 3 fellows
- Oncology Services ~3,000 cases per year
CCAH Oncology Program

2006-2011

• 33 Grants
  – $351,000
  – $70k/year

SINCE 2011

• 73 Grants
  – $779,000
  – $156k/year

Now consists of over 25 members in Surgery, Genetics, Bioinformatics, Neurology/Neurosurgery, Anatomic and Clinical Pathology, Radiology, Pharmacology
Oncology Services

- Medical Oncology
  - Four Faculty – Burton, Rebhun, Skorupski, Willcox
  - Five Residents
- Radiation Oncology
  - Three Faculty – Theon, Hansen, Kent
  - One Resident
- Surgical Oncology
  - 3 Faculty – Culp, Giuffrida, Steffey
- Basic Science
  - Xinbin Chen
  - Luke Wittenburg – pharmacology
  - Liz Sparger - Immunology
Collaborative Program

COTC Active Member

Industry
Omniox

Completed several studies looking at novel oxygen carrier
Current study – role of oxygen carrier in modulating immune response
Recent R01 - Development of PET imaging biomarkers to predict enhanced glioblastoma radiotherapy by a novel H-NOX oxygen carrier

Oncosec Medical – Investigation of IL-12 plasmid in sarcomas
MiniEXPLORER-1 – Intermediate-bore PET

Canine bone tumor 18F-FDG - osteosarcoma
MiniEXPLORER-2 – Intermediate-bore PET/CT (Should Arrive Summer 2017)
Capabilities

Radiation Therapy
- True Beam Linear Accelerator
- Collaboration with Physics group at UCDMC
Capabilities

Canine Immunotherapy Panels

[Graphs and charts illustrating various cell populations and data points related to canine immunotherapy panels.]
Two Campuses
ONE HEALTH, ONE VISION
One UCDavis
Comparative Oncology Program

Xinbin Chen, DVM, PhD
Professor of Oncology
Department of Surgical and Radiological Sciences
Schools of Medicine and Veterinary Medicine

Michael Kent, MAS, DVM
Professor of Radiation Oncology
Department of Surgical and Radiological Sciences
School of Veterinary Medicine
Institutional Grants

- CTSC
  - Training, K12, K30

- IRG (American Cancer Society)

- Pilot funding for collaborative projects
American Cancer Society Institutional Research Grant (IRG) award

Institutional Research Grant (IRG) Program

The Institutional Research Grant (IRG) program is made possible by funds awarded competitively by the American Cancer Society with additional funds provided by the Associate Dean for Research, UC Davis School of Medicine. The Principal Investigator is Primo Lara, Division of Hematology and Oncology, Department of Internal Medicine, UC Davis School of Medicine.

Institutional Research Grants serve as seed money for promising new projects or novel investigations from junior faculty such as assistant-level professors, researchers with adjunct appointments at the assistant level, or those in research series, or even to associate level faculty who meet additional requirements. Applicants must be within seven years of their initial academic appointment. Applications from eligible faculty in any school or college are welcome and applications in any area of cancer-related research – from basic science to clinical research to psychosocial research – are appropriate.

Investigators who have an active national peer-reviewed research grant are not eligible. Applicants can have one prior IRG award from UC Davis or from another institution. The short proposal is usually due in the fall with funding beginning the following year. Maximum funding is currently $40,000 for a one-year project. Award decisions are made intramurally by a committee of UC Davis faculty. Because awards are intramural, they are not processed through Sponsored Programs at the School of Medicine or through the Office of Research.

Questions may be directed to cancer.center@ucdmc.ucdavis.edu.
CTSC Training Grants

Mentored Clinical Research Training Program

The Mentored Clinical Research Training Program (MCRTP) provides a solid foundation for clinical/patient-oriented research for junior faculty, clinical and pre-clinical fellows, and post-doctoral scholars. The MCRTP centers around three core elements: didactic instruction, mentored research, and special experiences, leading to a Masters of Advanced Study (MAS) in Clinical Research.

The didactic instruction provides scholars a standardized set of skills critical to all types of clinical and translational research. The instruction includes a two year core curriculum and electives that can be tailored to best meet each scholar’s career development needs. The didactic curriculum is a combination of established and new courses explicitly designed for the MCRTP.

The mentored research experience is provided by senior faculty with strong track records of research funding and success. Mentors and scholars receive a special orientation and training to provide them with a consistent set of expectations for the mentored research experience.

The special experiences enhance the overall program by offering a highly engaging, interactive learning environment for scholars to network and set the groundwork for future collaborative, peer mentoring relationships, and research teams.

The annual scholar symposium is an opportunity for scholars to gather their experience and present their research to the External Advisory Board and the Clinical Research Graduate Group Members.

Junior faculty, advanced post-doctoral fellows, and senior clinical fellows are eligible to apply. Graduates from the MCRTP will be eligible for the UC Davis K12 Program.

Paul Calabresi Clinical Oncology K12 Program

This NIH-NCI funded program combines key didactic, research, and career development components to train independent and productive clinical oncology researchers. The curriculum is guided by two research tracks in Basic/Translational and Clinical science. Scholars participate in four training components: (1) core competencies, (2) advanced coursework, (3) career development, and (4) mentored research. The mentored research training plan will be supervised by two senior, independently funded faculty members (one Basic/Translational mentor and one Clinical mentor) who will guide the scholar in the development and conduct of his/her research project. Scholars are expected to have developed their own investigator-initiated clinical trial during the training period, and have plans to secure suitable funding to support it.

Mission

The goal of the program is to train junior faculty (basic-translational scientists and clinician scientists) as investigators in team-based, patient-oriented cancer research. Upon successful completion of a three-year, salary-supported core curriculum, scholars will receive a UC Davis Comprehensive Cancer Center Certificate in Clinical Cancer Research.
CO Program Overview

OVERVIEW

- Members: 36
- Departments: 16
- Schools: 4
- Publications (2010-2015): 723

12.9% Intra-Programmatic
31% Inter-Programmatic
~10% Multi-Institutional

FUNDING

- Peer-reviewed Direct Costs: $8.84 million
- Total Direct Costs: $9.55 million

- NCI: 30%
- Other NIH: 60%
- Other: 6%
- Other Non Peer-Reviewed: 4%

Peer-reviewed Direct Costs
Total Direct Costs
Canine model of convection-enhanced delivery of liposomes containing CPT-11 monitored with real-time magnetic resonance imaging

Laboratory investigation


Departments of Surgical and Radiological Sciences, and Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California, Davis; Department of Neurosurgery, Brain Tumor Research Center, University of California, San Francisco; †Hermes Biosciences, Inc., San Francisco; and ‡University of California at San Francisco Comprehensive Cancer Center, San Francisco, California

A selective high affinity ligand (SHAL) designed to bind to an over-expressed human antigen on non-Hodgkin's lymphoma also binds to canine B-cell lymphomas

Rod L. Balhorn, Katherine A. Skorupski, Saphon Hok, Monique Cosman Balhorn, Teri Guerrero, Robert B. Rehbun

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Research paper

Veterinary Immunology and Immunopathology 132 (2009) 235–242

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Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm


UCD
Combined Radiotherapy and Immunotherapy Using CPG ODNs and IDO Blockade

We evaluated this novel triple therapy in a canine clinical trial.

Well Tolerated

IDO up-regulation in the tumor microenvironment maintains immunosuppression after immunotherapy. Systemic IDO blockade may substantially improve treatment efficacy by limiting rebound immunosuppression within the tumor, thereby initiating a local anti-tumor immune response that exerts systemic effects.
Blocking Indolamine-2,3-Dioxygenase Rebound Immune Suppression Boosts Antitumor Effects of Radio-Immunotherapy in Murine Models and Spontaneous Canine Malignancies

Arta M. Monjazeb1, Michael S. Kent2, Steven K. Grossenbacher3, Christine Mair3, Anthony E. Zamora3, Annie Mirsoian3, Mingyi Chen3, Amir Kol5, Stephen L. Shiao6, Abhinav Reddy1, Julian R. Perks1, William T.N. Culp2, Ellen E. Spargur2, Robert J. Canter7, Gail D. Scise1, and William J. Murphy1,8

Abstract

Purpose: Previous studies demonstrate that intratumoral CpG immunotherapy in combination with radiotherapy acts as an in-situ vaccine inducing antitumor immune responses capable of eradicating systemic disease. Unfortunately, most patients fail to respond. We hypothesized that immunotherapy can paradoxically upregulate immunosuppressive pathways, a phenomenon we term "rebound immune suppression," limiting clinical responses. We further hypothesized that the immunosuppressive enzyme indolamine-2,3-dioxygenase (IDO) is a mechanism of rebound immune suppression and that IDO blockade would improve immunotherapy efficacy.

Experimental Design: We examined the efficacy and immunologic effects of a novel triple therapy consisting of local radiotherapy, intratumoral CpG, and systemic IDO blockade in murine models and a pilot canine clinical trial.

Results: In murine models, we observed marked increase in intratumoral IDO expression after treatment with radiotherapy, CpG, or other immunotherapies. The addition of IDO blockade to radiotherapy + CpG decreased IDO activity, reduced tumor growth, and reduced immunosuppressive factors, such as regulatory T cells in the tumor microenvironment. This triple combination induced systemic antitumor effects, decreasing metastases, and improving survival in a CD8+ T-cell–dependent manner. We evaluated this novel triple therapy in a canine clinical trial, because spontaneous canine malignancies closely reflect human cancer. Mirroring our murine studies, the therapy was well tolerated, reduced intratumoral immunosuppression, and induced robust systemic antitumor effects.

Conclusions: These results suggest that IDO maintains immune suppression in the tumor after therapy, and IDO blockade promotes a local antitumor immune response with systemic consequences. The efficacy and limited toxicity of this strategy are attractive for clinical translation. Clin Cancer Res 22(17): 4328–40. ©2016 AACR.
Single-energy computed tomography-based pulmonary perfusion imaging: Proof-of-principle in a canine model

- Personalized medicine project to develop technique to allow determination of areas of lung that differ between perfusion and ventilation allowing for decrease toxicity associated with lung tumor radiotherapy

Funding
RSNA

Publication
Med. Phys. 43, 3998

Collaborations
Yamamoto, Kent, Wisner, Boone (Inter)
Administrative Supplements for P30 Grant to Support Research in Canine Immunotherapy

• Collaboration of NCI-Designated Cancer Centers and Veterinary Medical Colleges. $318,472 Direct Costs; 13 investigators combining several programs

• Genomic Analysis of Canine High Grade Gliomas, Melanomas, and Osteosarcomas
  – Whole exome sequencing for analysis of non-synonymous somatic mutational load and RNAseq expression analysis for mutational load and DLA typing. 30 banked and 5 new samples.

• Immunophenotyping and Analysis of TME
• Program 2, Comparative Oncology Received “Excellent” status

• “The impression is that there are very few high impact papers that have come out of this program with senior leadership (i.e. higher impact than Blood or Cancer Research).”
Funding for Research in Translational and Comparative Canine Oncology: The UCD Experience

- Laying the groundwork – UCD Environment
  - Where UCD has been successful
    - CCAH
    - UCD CCC
      - Pilot collaborative funding
      - K12, K30
  - NIH grants
    - Training grants, K01, K08
    - RO1 grants
    - P30 Supplement
- Landscape of current NIH funding for canine cancer
  - Types of NIH funding
  - Institutions
- Examples of NIH funding at UCD
  - Specific aims/comparative mouse studies
  - Role of companion animal studies in these grants?
- Measures of success/Challenges
  - Lab/Trials personnel
  - Publications/Tenure
  - High impact research?
- Strategies for success
  - Including clinicians early in the grant-writing process
  - Including vets on basic research component
  - Proper budgeting
- Programmatic planning
  - Expansion/diversity of comparative oncology programs
  - Expectations for junior faculty
  - Expectations from Med schools
Measures of Success?

Veterinary Faculty

- Publications
  - Senior vs. middle author
  - Basic vs. clinical research
  - Stand alone dog papers?
  - Impact
- Salaries/Stipends/Overhead
  - Lab techs
  - post-docs
  - grad students
- Support/Grants
  - NIH – Co-investigator?
  - Philanthropic support
  - Foundation grants
- High Risk Clinical Studies
  - Clinical Design/IACUC approval
  - Time of accrual
  - Maturation of Data
  - Negative results publishable?
- Tenure

NIH/NCI/CTSC

- High impact publications
- NIH funding
- IND applications
- Translational success/impact

UC Davis Veterinary Medicine
Strategies for Success (identified pitfalls)

– Inclusion of clinical collaborators on basic research aims

– Including clinical collaborators in the grant-writing process

– Proper budgeting

– Incentive/Accountability (program review)

– Concurrent mouse and dog studies?
Summary and Final Thoughts

- Basic and translational canine cancer studies
- Most NIH funded R01’s include mouse and canine model, but some exceptions
- Need to recognize efforts of veterinarians in collaborative projects (promotion and tenure)
- Ideally, consider including veterinarians in planning, design, analysis of basic and (pre)clinical research components (all aims, not just the dog!)
- Pilot canine trials likely not publishable as stand-alone papers, perhaps they should be included with murine studies?
- Funding for technical support in the lab or clinical trials coordinators is a tremendous challenge.
Questions?

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