The University of Minnesota Animal Cancer Care and Research Program (ACCR) – Vision and Opportunities

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University of Minnesota
Driven to Discover℠
Disclosures

• None
What We Will Discuss

• ACCR vision, mission, and goals
  – Comparative oncology
• Resources
• UMN-Stanford collaborations
• Clinical studies and ongoing work
ACCR Vision

A world where we no longer fear cancer
What is ACCR?

- Fully integrates resources from a College of Veterinary Medicine (CVM) and The Masonic Cancer Center, University of Minnesota

UNIVERSITY OF MINNESOTA
Animal Cancer Care & Research Program
ACCR Program Mission

• Advance knowledge and translate it into delivery of care to reduce the impact of cancer in human and animal patients
ACCR Program Goals

• Identify and characterize causes and behavior of cancers that affect humans and animals

• Learn from models of naturally occurring cancers that occupy the interface between rodents and humans

• Seek outcomes that benefit humans and companion animals alike
Caseload

• Nearly 40,000 admissions/year
• Average oncology cases/year
  – 800 new, 600 rechecks, 2,000 chemotherapy patients, radiation therapy patients, add-ons
ACCR Facilities

- Medical Imaging
  - 3T MRI
  - 64-slice CT scanner
  - Located within the Veterinary Medical Center (VMC)
ACCR Facilities

• Medical Imaging
  – Siemens mCt-64 Biograph TrueD HD PET/CT scanner
  – Located within the Center for Clinical Imaging Research (CCIR)
ACCR Facilities

- Radiation Therapy
  - Varian Clinac iX, 6mv photon, 6-12 MeV electrons, 120 leaf MLC
  - Located within the VMC
ACCR Facilities

- Research Facilities
  - Molecular and Cellular Therapeutics
  - Located on the UMN St. Paul campus
ACCR Facilities

• Research Facilities
  – Masonic Cancer Center
  – Cancer and Cardiovascular Research Building (CCRB)
  – Located on the UMN Minneapolis campus
UMN-Stanford Collaborations

- Irv Weissman
- Jaime Modiano
  – Leading investigators

Eradication of Canine Diffuse Large B-Cell Lymphoma in a Murine Xenograft Model with CD47 Blockade and Anti-CD20

Kipp Weiskopf1,3,4, Katie L. Anderson5,6, Daikyu Ito5,6, Peter J. Schnorr3,3, Hirota Kinomura4,5, Aaron M. Ring2,3,7, Kristin Blonk5, Jem Efe5, Sarah Rue5, David Lowery5, Amira Barkal2,3, Susan Prohasza2,3,5, Kelly M. McKenna2,3, Ingrid Conti2,3, Timothy D. O’Brien3,4,5, M. Gerard O’Sullivan3,4, Irving L. Weissman1,3,4, and Jaime F. Modiano5,6,7

Abstract

Cancer immunotherapies hold much promise, but their potential in veterinary settings has not yet been fully appreciated. Canine lymphomas are among the most common tumors of dogs and bear remarkable similarity to human disease. In this study, we evaluated the combination of CD47 blockade with anti-CD20 passive immunotherapy for canine lymphoma. The CD47/SCRF1 axis is an immune checkpoint that regulates macrophage activation. In humans, CD47 is expressed on cancer cells and enables evasion from phagocytes. CD47 blocking therapies are now under investigation in clinical trials for a variety of human cancers. We found the canine CD47/SCRF1 axis to be conserved biochemically and functionally. We identified high-affinity SCRPs variants that antagonize canine CD47 and specific fusion proteins, these therapeutic agents exhibited single-agent efficacy in a murine xenograft model of canine lymphoma. As robust synergy between CD47 blockade and tumor-specific antibodies has been demonstrated for human cancer, we evaluated the combination of CD47 blockade with 1E4-1g8, a canine-specific antibody to CD20. 1E4-1g8 could elicit a therapeutic response against canine lymphoma in vivo as a single agent. However, augmented responses were observed when combined with CD47-blocking therapies, resulting in synergy in vivo and in vitro and eliciting cures in 100% of mice bearing canine lymphoma. Our findings support further testing of CD47-blocking therapies alone and in combination with CD20 antibodies in the veterinary setting. Cancer Immunol Res (2020).

Published OnlineFirst November 14, 2016; DOI: 10.1158/2326-6066.CIR-16-0155
UMN-Stanford Collaborations

- Larry Steinman
- PJ Utz
- Bill Robinson
- Jaime Modiano
  – Leading investigators
UMN-Stanford New Collaborations

• Bill Robinson
• Steve Galli
• Mike Conzemius
  – Leading investigators

• Examine the potential role of mast cells in osteoarthritis
UMN-Stanford New Collaborations

• More to come…
• Come talk to me!
EGF Bispecific Angiotoxin (eBAT)

Published OnlineFirst February 13, 2017; DOI: 10.1158/1535-7183.MCT-16-0637

Models and Technologies

Safe and Effective Sarcoma Therapy through Bispecific Targeting of EGFR and uPAR

Antonella Borgatti1,2,3, Joseph S. Koopmeiners3,4, Aaron L. Sarver5, Amber L. Winter5, Kathleen Stuebner5, Deborah Todhunter5,6, Anthony E. Rizzardi7, Jonathan C. Henriksen7, Stephen Schmechel7, Colleen L. Forster8, Jong-Hyuk Kim1,2,3, Jerry Froelich9, Jillian Walz9,12, Michael S. Henson3,12,3, Matthew Breen10,11, Kerstin Lindblad-Toh12,13, Felix Oh6, Kristy Pilbeam14, Jaime F. Modiano1,2,3,15,16, and Daniel A. Vallera1,3,6

Abstract

Sarcomas differ from carcinomas in their mesenchymal origin. Therapeutic advancements have come slowly, so alternative drugs and models are urgently needed. These studies report a new drug for sarcomas that simultaneously targets both tumor and tumor neovasculation. eBAT is a bispecific angiotoxin consisting of truncated, deimmunized Pseudomonas exotoxin fused to EGF and the amino terminal fragment of urokinase. Here, we study the drug in an in vivo “ontarget” companion dog trial as eBAT effectively kills canine hemangiosarcoma and human sarcoma cells in vitro. We reasoned the model has value due to the common occurrence of spontaneous sarcomas in dogs and a limited lifespan allowing for rapid accrual and data collection. Splenectomized dogs with minimal residual disease were given one cycle of eBAT followed by adjuvant doxorubicin in an adaptive dose-finding, phase I-II study of 23 dogs with spontaneous, stage I-II, splenic hemangiosarcoma. eBAT improved 6-month survival from <40% in a comparison population to approximately 70% in dogs treated at a biologically active dose (50 μg/kg). Six dogs were long-term survivors, living >450 days. eBAT abated expected toxicity associated with EGFR targeting, a finding supported by mouse studies. Urokinase plasminogen activator receptor and EGFR are targets for human sarcomas, so thorough evaluation is crucial for validation of the dog model. Thus, we validated these markers for human sarcoma targeting in the study of 212 human and 97 canine sarcoma samples. Our results support further translation of eBAT for human patients with sarcomas and perhaps other EGFR-expressing malignancies. Mol Cancer Ther; 16(5): 956–65. ©2017 AACR.
eBAT Kills Sarcoma Cells

Emma Canine Hemangiosarcoma

U-20S Osteosarcoma

AS5 Angiosarcoma

HPB-MLT T Cell Leukemia

- EGF
- L
- ATF
- dPE38

pEGFATF.pET21d

Nco1
hma
EASGGPE
KDEL
NotI

Emma Canine Hemangiosarcoma

IC50 = 0.008

CD3CD3KDEL

U-20S Osteosarcoma

EGF4KDEL Clinical IC50 = 0.002

AS5 Angiosarcoma

IC50 = 0.40

19KDEL IC50 not reached

HPB-MLT T Cell Leukemia

eBAT IC50 not reached

EGF4KDEL

eBAT Kills Sarcoma Cells
Sarcomas Express eBAT Targets

- Human sarcomas express epidermal growth factor receptor and urokinase receptor

Human Patients TCGA
## Canine Clinical Study (SRCBST)

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<tr>
<th>Splenectomy</th>
<th>eBAT</th>
<th>eBAT</th>
<th>eBAT</th>
<th>Recheck</th>
<th>Doxorubicin</th>
<th>Recheck, Doxorubicin</th>
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### Dose Level

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<th>Dose Level</th>
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<tr>
<td>1 (25 ug/kg)</td>
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<tr>
<td>2 (50 ug/kg)</td>
<td>17</td>
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<tr>
<td>3 (100 ug/kg)</td>
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</table>
eBAT Shows Limited Toxicity *in vivo*

Description of adverse events (AEs) in individual dogs, management, and outcome

<table>
<thead>
<tr>
<th>Dog ID and Breed</th>
<th>Dose Level</th>
<th>AEs</th>
<th>Management</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>MN* 11 Cairn terrier</td>
<td>2</td>
<td>Grade 3 ALT elevation after 1st infusion</td>
<td>Second eBAT infusion delayed one week</td>
<td>Full recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotensive event* during 2nd infusion</td>
<td>IV fluid bolus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotensive event* during 2nd infusion</td>
<td>3rd eBAT infusion not administered</td>
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<tr>
<td>MN 17 Labrador retriever</td>
<td>2</td>
<td>Hypotensive event followed by a seizure during 1st infusion</td>
<td>IV fluid bolus, infusion restated 45 minutes later with no complications</td>
<td>Full recovery</td>
</tr>
<tr>
<td>MN 22 rat terrier</td>
<td>2</td>
<td>Grade 2 ALT elevation after 1st infusion</td>
<td>Monitoring</td>
<td>Full recovery</td>
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<tr>
<td>MN 07 Newfoundland</td>
<td>3</td>
<td>Hypotensive event at the end of 3rd infusion</td>
<td>IV fluid bolus</td>
<td>Full recovery</td>
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<tr>
<td>MN 09 Goldendoodle</td>
<td>3</td>
<td>Hypotensive event during second infusion</td>
<td>IV fluid bolus, infusion not restarted</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>
**eBAT Shows Limited Toxicity *in vivo***

Summary of death events in normal mice treated with ligand specific toxins

<table>
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<tr>
<th>Treatment</th>
<th>Observed Deaths (%)</th>
<th>Dose (µg/kg)</th>
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<tbody>
<tr>
<td>Treatment</td>
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<td>20</td>
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<td>40</td>
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<tr>
<td></td>
<td></td>
<td>80</td>
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<tr>
<td></td>
<td></td>
<td>160</td>
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<tr>
<td>Monospecific EGF-toxin</td>
<td>0/8 (0)</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td></td>
<td>6/8 (75)</td>
<td>8/8 (100)</td>
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<tr>
<td></td>
<td>8/8 (100)</td>
<td></td>
</tr>
<tr>
<td>Monospecific uPA-toxin,</td>
<td>0/8 (0)</td>
<td>0/8 (0)</td>
</tr>
<tr>
<td></td>
<td>2/8 (25)</td>
<td>8/8 (100)</td>
</tr>
<tr>
<td></td>
<td>8/8 (100)</td>
<td></td>
</tr>
<tr>
<td>Monospecific EGF-toxin +</td>
<td>0/7 (0)</td>
<td>1/7 (14)</td>
</tr>
<tr>
<td>monospecific uPA-toxin</td>
<td></td>
<td>2/7 (29)</td>
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<tr>
<td></td>
<td></td>
<td>7/7 (100)</td>
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<tr>
<td></td>
<td></td>
<td>7/7 (100)</td>
</tr>
<tr>
<td>eBAT</td>
<td>0/8 (0)</td>
<td>0/8 (0)</td>
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</table>
eBAT is Safe and Potentially Effective in Dogs with Spontaneous Hemangiosarcoma (HSA)
Lesions most consistent with HSA in 2/9 dogs
- Right atrium and liver
- Lesions were not visible on conventional diagnostics
Immune System Engagers

IL15 Trispecific Killer Engagers (TriKE) Make Natural Killer Cells Specific to CD33⁺ Targets While Also Inducing Persistence, In Vivo Expansion, and Enhanced Function


Abstract

Purpose: The effectiveness of NK cell infusions to induce leukemic remission is limited by lack of both antigen specificity and in vivo expansion. To address this first issue, we previously generated a bispecific killer engager (BiKE) containing single-chain scFv against CD16 and CD33 to create an immunologic synapse between NK cells and CD33⁺ myeloid targets. We have now incorporated a novel modified human IL15 coxsackievirus, producing a 161533 trispecific killer engager (TriKE) to induce expansion, priming, and survival, which we hypothesize will enhance clinical efficacy.

Experimental Design: Reagents were tested in proliferation and functional assays and in an in vivo xenograft model of AML.

Results: When compared with the 1633 BiKE, the 161533 TriKE induced superior NK cell cytotoxicity, degranulation, and cytokine production against CD33⁺-HL-60 targets, and increased NK survival and proliferation. Specificity was shown by the ability of a 16153Pcam TriKE to kill CD33-EpCAM⁺ targets. Using NK cells from patients after allogeneic stem cell transplantation when NK cell function is defective, the 161533 TriKE restored potent NK function against primary AML targets and induced specific NK cell proliferation. These results were confirmed in an immunodeficient mouse HL-60-Luc tumor model where the 161533 TriKE exhibited superior antitumor activity and induced in vivo persistence and survival of human NK cells for at least 3 weeks.

Conclusions: Off-the-shelf 161533 TriKE imparts antigen specificity and promotes in vivo persistence, activation, and survival of NK cells. These qualities are ideal for NK cell therapy of myeloid malignancies or targeting antigens of solid tumors.

Clin Cancer Res. 22(14): 3440-50, ©2016 AACR.

See related commentary by Tabanov, s. 5419.
Immune System Engagers

- Sarcoma Trispecific NK Cell Engager (STriKe)
  - Kills sarcoma cells (SAOS2) \textit{in vitro}
  - Induces NK cell expansion
Summary

• We have developed stable resources to maintain and expand the ACCR program in a position of national/int’l leadership and productivity

• We have a commitment to continue to make a difference for better health

• We encourage collaborations for the conduction of projects in concordance with our mission, vision, and goals