

10. Kim JH, Graef AJ, Dickerson EB, Modiano JF. Pathobiology of hemangiosarcoma in dogs: research advances and future perspectives. *Vet Sci* 2015; 2:388–405.
11. Lamerato-Kozicki AR, Helm KM, Jubala CM, Cutter GC, Modiano JF. Canine hemangiosarcoma originates from hematopoietic precursors with potential for endothelial differentiation. *Exp Hematol* 2006;34:870–8.
12. Liu L, Kakiuchi-Kiyota S, Arnold LL, Johansson SL, Wert D, Cohen SM. Pathogenesis of human hemangiosarcomas and hemangiomas. *Human Pathol* 2013;44:2302–11.
13. Andersen NJ, Froman RE, Kitchell BE, Duesbery NS. Clinical and molecular biology of angiosarcoma. In: Derbel PF, editor. *Soft tissue tumors*. Rijeka, Croatia: InTech; 2011.
14. Buehler D, Rice SR, Moody JS, Rush P, Hafez GR, Attia S, et al. Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. *Am J Clin Oncol* 2014;37:473–9.
15. Wendelburg KM, Price LL, Burgess KE, Lyons JA, Lew FH, Berg J. Survival time of dogs with splenic hemangiosarcoma treated by splenectomy with or without adjuvant chemotherapy: 208 cases (2001–2012). *J Am Vet Med Assoc* 2015;247:393–403.
16. Gardner HL, London CA, Portela RA, Nguyen S, Rosenberg MP, Klein MK, et al. Maintenance therapy with toceranib following doxorubicin-based chemotherapy for canine splenic hemangiosarcoma. *BMC Vet Res* 2015;11:131.
17. Albritton KH, Randall RL. Prospects for targeted therapy of synovial sarcoma. *J Pediatr Hematol Oncol* 2005;27:219–22.
18. Yang JL, Hannan MT, Russell PJ, Crowe PJ. Expression of HER1/EGFR protein in human soft tissue sarcomas. *Eur J Surg Oncol* 2006;32:466–8.
19. Tschöep K, Kohlmann A, Schlemmer M, Haferlach T, Issels RD. Gene expression profiling in sarcomas. *Crit Rev Oncol Hematol* 2007;63: 111–24.
20. Benassi MS, Ponticelli F, Azzoni E, Gamberi G, Pazzaglia L, Chiechi A, et al. Altered expression of urokinase-type plasminogen activator and plasminogen activator inhibitor in high-risk soft tissue sarcomas. *Histol Histopathol* 2007;22:1017–24.
21. Mazar AP, Ahn RW, O'Halloran TV. Development of novel therapeutics targeting the urokinase plasminogen activator receptor (uPAR) and their translation toward the clinic. *Curr Pharm Des* 2011;17:1970–8.
22. Schappa JT, Frantz AM, Gorden BH, Dickerson EB, Valleria DA, Modiano JF. Hemangiosarcoma and its cancer stem cell subpopulation are effectively killed by a toxin targeted through epidermal growth factor and urokinase receptors. *Int J Cancer* 2013;133:1936–44.
23. Waldron NN, Oh S, Valleria DA. Bispecific targeting of EGFR and uPAR in a mouse model of head and neck squamous cell carcinoma. *Oral Oncol* 2012;48:1202–7.
24. Gorden BH, Kim JH, Sarver AL, Frantz AM, Breen M, Lindblad-Toh K, et al. Identification of three molecular and functional subtypes in canine hemangiosarcoma through gene expression profiling and progenitor cell characterization. *Am J Pathol* 2014;184:985–95.
25. Tonomura N, Elvers I, Thomas R, Megquier K, Turner-Maier J, Howald C, et al. Genome-wide association study identifies shared risk loci common to two malignancies in golden retrievers. *PLoS Genet* 2015;11:e1004922.
26. Temiz NA, Moriarity BS, Wolf NK, Riordan JD, Dupuy AJ, Largaespada DA, et al. RNA sequencing of Sleeping Beauty transposon-induced tumors detects transposon-RNA fusions in forward genetic cancer screens. *Genome Res* 2016;26:119–29.
27. Sarver AE, Sarver AL, Thayanithy V, Subramanian S. Identification, by systematic RNA sequencing, of novel candidate biomarkers and therapeutic targets in human soft tissue tumors. *Lab Invest* 2015;95:1077–88.
28. Charbonneau B, Vogel RI, Manivel JC, Rizzardi A, Schmechel SC, Ognjanovic S, et al. Expression of FGFR3 and FGFR4 and clinical risk factors associated with progression-free survival in synovial sarcoma. *Hum Pathol* 2013;44:1918–26.
29. Tamburini BA, Trapp S, Phang TL, Schappa JT, Hunter LE, Modiano JF. Gene expression profiles of sporadic canine hemangiosarcoma are uniquely associated with breed. *PLoS One* 2009;4:e5549.
30. Li L, Sarver AL, Alamgir S, Subramanian S. Downregulation of microRNAs miR-1, -206 and -29 stabilizes PAX3 and CCND2 expression in rhabdomyosarcoma. *Lab Invest* 2012;92:571–83.
31. Huang X, Park H, Greene J, Pao J, Mulvey E, Zhou SX, et al. IGF1R- and ROR1-Specific CART Cells as a Potential Therapy for High Risk Sarcomas. *PLoS One* 2015;10:e0133152.
32. Scott MC, Sarver AL, Tomiyasu H, Cornax I, Van Etten J, Varshney J, et al. Aberrant retinoblastoma (RB)-E2F transcriptional regulation defines molecular phenotypes of osteosarcoma. *J Biol Chem* 2015;290:28070–83.
33. Koopmeiners JS, Modiano J. A Bayesian adaptive Phase I-II clinical trial for evaluating efficacy and toxicity with delayed outcomes. *Clin Trials* 2014; 11:38–48.
34. Vail DM. Veterinary co-operative oncology group - common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.0. *Vet Comp Oncol* 2004;2:195–213.
35. Hinchcliff KW, DiBartola SP. Quality matters: publishing in the era of CONSORT, REFLECT, and EBM. *J Vet Intern Med* 2010;24:8–9.
36. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013.
37. Stish BJ, Oh S, Chen H, Dudek AZ, Kratzke RA, Valleria DA. Design and modification of EGF4KDEL 7Mut, a novel bispecific ligand-directed toxin, with decreased immunogenicity and potent anti-mesothelioma activity. *Br J Cancer* 2009;101:1114–23.
38. Oh S, Stish BJ, Sachdev D, Chen H, Dudek AZ, Valleria DA. A novel "reduced immunogenicity" bispecific targeted toxin simultaneously recognizing human EGF and IL-4 receptors in a mouse model of metastatic breast carcinoma. *Clin Cancer Res* 2009;15:6137–47.
39. Pai LH, Wittes R, Setser A, Willingham MC, Pastan I. Treatment of advanced solid tumors with immunotoxin LMB-1: an antibody linked to Pseudomonas exotoxin. *Nat Med* 1996;2:350–3.
40. Bachanova V, Frankel AE, Cao Q, Lewis D, Grzywacz B, Verneris MR, et al. Phase I study of a bispecific ligand-directed toxin targeting CD22 and CD19 (DT2219) for refractory B-cell malignancies. *Clin Cancer Res* 2015;21: 1267–72.
41. Smallshaw JE, Ghetie V, Rizo J, Fulmer JR, Trahan LL, Ghetie MA, et al. Genetic engineering of an immunotoxin to eliminate pulmonary vascular leak in mice. *Nat Biotechnol* 2003;21:387–91.
42. Onda M, Nagata S, FitzGerald DJ, Beers R, Fisher RJ, Vincent JJ, et al. Characterization of the B cell epitopes associated with a truncated form of Pseudomonas exotoxin (PE38) used to make immunotoxins for the treatment of cancer patients. *J Immunol* 2006;177:8822–34.
43. Frankel AE, Woo JH, Ahn C, Foss FM, Duvic M, Neville PH, et al. Resimmune, an anti-CD3ε recombinant immunotoxin, induces durable remissions in patients with cutaneous T-cell lymphoma. *Haematologica* 2015;100:794–800.
44. Thamm DH. Miscellaneous tumors. In: Withrow SJ, Vail DM, Page RL, editors. *Withrow and MacEwen's small animal clinical oncology*. 5th ed. St. Louis, MO: Elsevier; 2013. p. 679–688.
45. Clifford CA, Mackin AJ, Henry CJ. Treatment of canine hemangiosarcoma: 2000 and beyond. *J Vet Intern Med* 2000;14:479–85.
46. Lana S, U'Ren L, Plaza S, Elmslie R, Gustafson D, Morley P, et al. Continuous low-dose oral chemotherapy for adjuvant therapy of splenic hemangiosarcoma in dogs. *J Vet Intern Med* 2007;21:764–9.
47. U'Ren LW, Biller BJ, Elmslie RE, Thamm DH, Dow SW. Evaluation of a novel tumor vaccine in dogs with hemangiosarcoma. *J Vet Intern Med* 2007;21:113–20.
48. Vail DM, MacEwen EG, Kurzman ID, Dubielziq RR, Helfand SC, Kisseberth WC, et al. Liposome-encapsulated muramyl tripeptide phosphatidylethanolamine adjuvant immunotherapy for splenic hemangiosarcoma in the dog: a randomized multi-institutional clinical trial. *Clin Cancer Res* 1995; 1:1165–70.
49. Kreitman RJ, Tallman MS, Robak T, Coutre S, Wilson WH, Stetler-Stevenson M, et al. Phase I trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox (CAT-8015 or HA22) in patients with hairy cell leukemia. *J Clin Oncol* 2012;30:1822–8.
50. Anwar S, Yanai T, Sakai H. Immunohistochemical detection of urokinase plasminogen activator and urokinase plasminogen activator receptor in canine vascular endothelial tumours. *J Comp Pathol* 2015;153: 278–82.
51. Kim JH, Frantz AM, Anderson KL, Graef AJ, Scott MC, Robinson S, et al. Interleukin-8 promotes canine hemangiosarcoma growth by regulating the tumor microenvironment. *Exp Cell Res* 2014;323:155–64.
52. Tamburini BA, Phang TL, Fosmire SP, Scott MC, Trapp SC, Duckett MM, et al. Gene expression profiling identifies inflammation and angiogenesis as distinguishing features of canine hemangiosarcoma. *BMC Cancer* 2010;10:619.

Molecular Cancer Therapeutics

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

Antonella Borgatti, Joseph S. Koopmeiners, Aaron L. Sarver, et al.

Mol Cancer Ther 2017;16:956-965. Published OnlineFirst February 13, 2017.

Updated version Access the most recent version of this article at:
doi:[10.1158/1535-7163.MCT-16-0637](https://doi.org/10.1158/1535-7163.MCT-16-0637)

Supplementary Material Access the most recent supplemental material at:
<http://mct.aacrjournals.org/content/suppl/2017/02/13/1535-7163.MCT-16-0637.DC1>

Cited articles This article cites 49 articles, 10 of which you can access for free at:
<http://mct.aacrjournals.org/content/16/5/956.full#ref-list-1>

Citing articles This article has been cited by 4 HighWire-hosted articles. Access the articles at:
<http://mct.aacrjournals.org/content/16/5/956.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://mct.aacrjournals.org/content/16/5/956>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.