BIOGRAPHICAL SKETCH

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NAME: **Brekken, Rolf A**

eRA COMMONS USER NAME (agency login): rbrekken

POSITION TITLE: **Professor of Surgery and Pharmacology**

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Luther College, Decorah, IA	BA	1991	Biology
Drake University, Des Moines, IA		1993	Immunology
UT Southwestern Medical Center, Dallas, TX	PhD	1999	Cell and Molecular Biology
The Hope Heart Institute, Seattle, WA	Postdoctoral Fellow	2002	Vascular Biology

A. Personal Statement

I trained as a vascular biologist with an emphasis on tumor angiogenesis. For the last 24 years I have studied the function and contribution of the tumor microenvironment to tumor progression and drug response. Animal models of pancreatic, breast and lung cancer have been the major focus of my group during this time. We have active research programs on how epithelial plasticity and extracellular matrix signaling contribute to tumor progression. We also have active investigations on immune activation strategies for tumor therapy, one of these strategies (the phosphatidylserine targeting antibody, bavituximab) was tested clinically at UTSW (NCT03519997, PMID:38467639). We have also validated Axl as a therapeutic target in pancreatic cancer and this advanced to clinical testing in pancreatic cancer patients at UTSW (NCT03649321).

I have also been active in educating trainees, such that over 45 current or former mentees have trained in my laboratory. Currently there is 1 PhD trainee trainee in my group. Former trainees include 17 graduate students (16 PhD, 1 Masters student from Germany), 12 postdocs, 3 pediatric hematology oncology fellows, 1 medical oncology fellow and 10 surgery residents. More than 20 former trainees are now in research intensive careers or training and 17 are in research-related fields. I am Director of the Cancer Biology Graduate program and was a member of Graduate Student Advisory Committee (2012-2020). I am also Deputy Director of the Hamon Center for Therapeutic Oncology Research. Additionally, I am Program Director and PI of the Translational Cancer Biology T32 (NCI T32 CA291654), was on the Executive Committee for the Physician Scientist Oncology Training T32 (PI: S. Skapek, NCI T32 CA136515, 2016-2019) and am a member of the Simmons Comprehensive Cancer Center Education and Training Committee. Outside of UT Southwestern, I am on the board (Ex Officio) of CABTRAC (past-President) and am a member of the EAB for 5 training grants (NCI T32 CA257923 (PI: Siemann), U of Florida; Cancer Research Training Program (CPRIT), UT Health San Antonio; NCI T32 CA148724 (PI: Z. Sun), UT Health San Antonio; NCI T32 CA009213 (PIs: Carew & Curiel-Lewandrowski), University of Arizona Cancer Center; NCI T32 CA009109 (PIs: Dudley & Rutowski), University of Virginia). I was a standing member of the Developmental Therapeutics study section for the CSR/NIH until June 2017 and maintained continuous submission privileges thru ad hoc service for the NIH until September 2021. I also review frequently for other funding organizations including the American Cancer Society, METAvivor and the European Research Council.

Ongoing projects that I would like to highlight include:

R21CA286348 (Brekken) 06/2024 – 05/2026
Inhibition of pleiotrophin to combat pancreatic cancer metastasis

DP240244 (7 Hills Pharma) 03/2026-12/31/2026
Evaluation of 7HP935 to augment tissue selective homing and augment of anti-neoplastic activity

Flow Through from 7 Hills Pharma

R01EB034360 (Obaid) 07/2024 – 06/2028
Molecular Imaging Guidance for Potentiating Chemoimmunotherapy in Pancreatic Cancer using Photodynamic Priming
Role: Co-Investigator

Citations: Graduate trainees; postdoctoral/clinical trainees
Arner EN, Alzhanova D, Westcott JM, Hinz S, Tiron CE, Blo M, Mai A, Virtakoivu R, Phinney N, Nord S, Aguilera KY, Rizvi A, Toombs JE, Reese T, Fey V, Mickem D, Gausdal G, Ivaska J, Lorens* JB and Brekken* RA. AXL-TBK1 driven nuclear AKT3 promotes EMT. Science Signaling 2024 17:eado6057 PMID: 39689180 PMCID: PMC12229235

Phinney NZ, Toombs JE, Huang X, and **Brekken RA**. Development of betabodies: the next generation of phosphatidylserine targeting agents. Journal of Biological Chemistry 2024 300:107681. PMID: 39159812 PMCID: PMC11416255

Ganguly D, Schmidt MO, Coleman M, Ngo T-V C, Sorrelle N, Dominguez ATA, Murimwa GZ, Toombs JE, Lewis C, Fang YV, Valdes-Mora F, Gallego-Ortega D, Wellstein A and Brekken RA. Pleiotrophin drives a pro-metastatic immune niche in breast cancer. Journal of Experimental Medicine, 2023 220:e20220610 PMID: 36828390 PMCID: PMC9998964

Huang H, Wang Z, Zhang Y, Pradhan RN, Ganguly D, Chandra R, Murimwa G, Wright S, Gu X, Maddipati R, Muller S, Turley SJ and Brekken RA. Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory T cells in pancreatic cancer. Cancer Cell 2022 40:656-673. PMID: 35523176 PMCID: PMC9197998

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2026	Chair, NIH study section SEP ZRG1 CDPT-Z (02)
2025	Chair, NIH study section SEP F09C (20), ad hoc member of two other NIH study sections
2025	Past-President, CABTRAC
2024	November: CIMER workshop on 'Articulating your mentoring philosophy'
2024	Ad hoc DoD review: LCRP CON-IIT
2024	Ad hoc NIH review: ZRG1 CDPT-L (02) M
2024	President, CABTRAC
2023	ERC Advanced Grant panel, LS4
2023 - present	EAB, NCI T32 CA148724 (PI: Z. Sun), UT Health San Antonio
2022	President Elect & Secretary, CABTRAC
2022	Ad hoc NIH review: NCI ZRG1 BTC-W (80)
2021	ERC Advanced Grant panel, LS4
2021	Ad hoc NIH review: NCI F; ZRG1 OBT-D (02) (chair); ZCA1 SRB-A (02); ZRG1 OBT-R (55); Mechanisms of Cancer Therapeutics-2 (MCT-2);
2021 - present	Editorial board, *Cancer Research*
2021 - present	EAB, Cancer Research Training Program (CPRIT), UT Health San Antonio
2020	Ad hoc NIH review: ZCA1 RPRB-H (J1) (P01 co-chair); NCI-A RTRB-O (S1) P NCI site visit; ZRG1 OBT-R
2020 - present	EAB, NCI T32 CA257923 (PI: Siemann), U of Florida
2020 - 2024	Council Member, American Society for Matrix Biology
2020 - present	Editorial board, *Matrix Biology* & *Matrix Biology Plus*
2019 - 2022	Consultant, Vigeo Therapeutics, Inc
2019 - 2020	AACR TME Steering Committee
2019	Ad hoc NIH review: ZCA1 SRB-5 (J1) (P01, co-chair); ZRG1 OBT-D (02) (chair); ZRG1 OBT-D (chair); ZCA1 RPRB-F (M1) P01

2019 - 2022	Board of Directors, CABTRAC
2019	ERC Advanced Grant panel, LS4
2018 - 2021	Vice Chair for Research, Department of Surgery, UT Southwestern
2018 - present	Director, Cancer Biology Graduate Program, UT Southwestern
2018 - 2022	Editorial board, *Cancers*
2017	ERC Advanced Grant panel, LS4
2016 – 2019	Executive Committee, Physician Scientist Oncology Training T32, NCI T32 CA136515 (PI: Skapek), UT Southwestern
2016 - 2018	Ad hoc NIH review for 8 study sections/SEPs
2015 - 2020	American Cancer Society, CSM study section
2015 - present	Deputy Director, Hamon Center for Therapeutic Oncology Research, UT Southwestern
2015 - present	Professor, UT Southwestern, Departments of Surgery and Pharmacology, Dallas, TX
2014 - 2021	Member, Research Council, Department of Surgery, UT Southwestern
2014 - 2017	Co-founder, Tuevol Therapeutics
2013 - 2017	NIH Review, Charter member, *Developmental Therapeutics* (DT)
2013 - present	Co-Leader, Tumor Microenvironment and Immunotherapy theme, Experimental Therapeutics Program, Simmons Comprehensive Cancer Center, UT Southwestern
2012 - 2017	Senior Editor, *Cancer Research*
2010 - 2012	Editorial board, *Cancer Research*
2009	Member, Angiogenesis, Microcirculation, and Cellular microenvironment subcommittee, Tumor Biology Section, 2009 AACR Annual Meeting Program committee
2009 - 2015	Associate Professor, UT Southwestern, Depts of Surgery and Pharmacology, Dallas, TX
2006 - 2012	Editorial board, *Experimental Biology and Medicine*
2002 - 2009	Assistant Professor, UT Southwestern, Departments of Surgery and Pharmacology, Dallas, TX
2002 -	Principal Investigator, Hamon Center for Therapeutic Oncology Research, UT Southwestern
2002 -	Member, Simmons Comprehensive Cancer Center, UT Southwestern
2002 –	Member, Cancer Biology and Integrative Biology Graduate Programs, UT Southwestern Graduate School of Biomedical Sciences, Dallas, TX
2000 - 2017	Consultant, Peregrine Pharmaceuticals
-	Member, American Association for the Advancement of Science
-	Member, American Association for Cancer Research
-	Member, American Society for Matrix Biology
-	Member, North American Vascular Biology Organization
-	Member, Society for Immunotherapy of Cancer
-	Member, Society for Leukocyte Biology
-	Member, American Society for Biochemistry and Molecular Biology

Honors

2016	Distinguished Service Award, Luther College
2011	Attendee, Harry and Elsa Jiler ACS Professor Meeting
2009	Kavli Fellow, Kavli Foundation and the NAS
2002	Junior Investigator Award, ACS/Simmons Cancer Center
2002	Effie Marie Cain Research Scholar in Angiogenesis Research, UT Southwestern
2000	Postdoctoral Fellowship, NIH NRSA, F32-HL10352
1994	Pre-doctoral Research Fellow, NIH Pharmacological Sciences Training Grant

C. Contribution to Science (208 primary data manuscripts; H index 99)

I. Development of therapeutic anti-VEGF antibodies. I developed unique antibody tools that have been useful in blocking VEGF and probing VEGF biology in complex systems.

1. Brekken RA, Huang X, King SW, Thorpe PE. Vascular endothelial growth factor as a marker of tumor endothelium. Cancer Res. 1998 May 1;58(9):1952-9. PubMed PMID: 9581838.
2. Brekken RA, Overholser JP, Stastny VA, Waltenberger J, Minna JD, et al. Selective inhibition of vascular endothelial growth factor (VEGF) receptor 2 (KDR/Flk-1) activity by a monoclonal anti-VEGF antibody blocks tumor growth in mice. Cancer Res. 2000 Sep 15;60(18):5117-24. PubMed PMID: 11016638.

3. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol. 2000 Oct;2(10):737-44. PubMed PMID: 11025665; PubMed Central PMCID: PMC2852586.
4. Joint inventor on **8** United States Patents directed to antibody and immunoconjugate compositions and methods for treating cancer, ocular and other angiogenic diseases by selectively inhibiting VEGF binding to VEGF receptor 2 (KDR/Flk-1). Also joint inventor on 13 counterpart international patents and 12 counterpart European patents in this portfolio.

II. Phosphatidylserine as a target for immune therapy. As a PhD student, I jointly developed the idea and performed initial experiments validating phosphatidylserine (PS) as a target expressed selectively on tumor endothelial cells. Antibodies that target PS were subsequently developed, found to block PS signaling and induce activation of innate and adaptive anti-tumor activity and are now in clinical development.

1. Thorpe PE, Ran S, Brekken RA. Cancer treatment methods using therapeutic conjugates that bind to aminophospholipids. US Patent # 6,312,694, Issue Date, 06 November 2001.
2. Beck AW, Luster T, Miller AF, Holloway SE, Conner CR, Barnett CC, Thorpe PE, Fleming JB and Brekken RA. Combination of a monoclonal anti-phosphatidylserine antibody with gemcitabine strongly inhibits the growth and metastasis of orthotopic pancreatic tumors in mice. Int. J. Cancer 2006 118:2639-2643. PubMed PMID: 16353142
3. Hsiehchen D, Beg MS, Kainthla R, Lohrey J, Kazmi SM, Khosama L, Maxwell MC, Kline H, Katz C, Kubota N, Siglinsky E, Pillai AK, Yuossoufian H, Mockbee C, Culm K, Uhlik M, Benjamin L, Brekken RA, Ahn C, Singal AG, Zhu H, Hoshida Y, Yopp AC Phase 2 trial of bavituximab, a phosphatidylserine targeting antibody, plus pembrolizumab in unresectable hepatocellular carcinoma. Nature Comm 2024 15:2178 PMID: 38467639, PMCID PMC10928173
4. Medina CB, Sobierajska E, Gong M, McManus DT, Thapa M, Lee J, Im SJ, Toombs JE, Mitchell JM, Wang Y, Carlise JW, Freeman GJ, Master VA, Ramalingam SS, Kissick HT, Li S, Brekken RA and Ahmed R. Exposed phosphatidylserine is an inhibitory molecule in T cell exhaustion. Nature 206 653:879-887. PMID: 41882354

III. VEGF and immune cell recruitment and activity. We discovered that VEGFR2 is expressed on a subset of macrophages only in tumor-bearing animals and are currently exploring the functional contribution of macrophage VEGFR2 and the pathways that induce VEGFR2 expression on macrophages to metastasis.

1. Dineen SP, Lynn KD, Holloway SE, Miller AF, Sullivan JP, et al. Vascular endothelial growth factor receptor 2 mediates macrophage infiltration into orthotopic pancreatic tumors in mice. Cancer Res. 2008 Jun 1;68(11):4340-6. PubMed PMID: 18519694.
2. Roland CL, Dineen SP, Lynn KD, Sullivan LA, Dellinger MT, et al. Inhibition of vascular endothelial growth factor reduces angiogenesis and modulates immune cell infiltration of orthotopic breast cancer xenografts. Mol Cancer Ther. 2009 Jul;8(7):1761-71. PubMed PMID: 19567820.
3. Roland CL, Lynn KD, Toombs JE, Dineen SP, Udugamasooriya DG, et al. Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer. PLoS One. 2009 Nov 3;4(11):e7669. PubMed PMID: 19888452; PubMed Central PMCID: PMC2766251.
4. Zhang Y, Huang H, Coleman M, Ziemys A, Gopal P, Kazmi SM and Brekken RA. VEGFR2 activity on myeloid cells mediates immune suppression in the tumor microenvironment. JCI Insight 2021 e150735 PMID: 34673569 PMCID: PMC8675197

IV. ECM signaling in the tumor microenvironment. We have identified that matricellular proteins are critical for control of ECM signaling in tumors. The matricellular proteins SPARC and Fbln5 reduce signaling induced by collagens and fibronectin, respectively, thereby directly affecting tumor cell survival, response to therapy and metastasis.

1. Schluterman MK, Chapman SL, Korpanty G, Ozumi K, Fukai T, et al. Loss of fibulin-5 binding to beta1 integrins inhibits tumor growth by increasing the level of ROS. Dis Model Mech. 2010 May-Jun;3(5-6):333-42. PubMed PMID: 20197418; PubMed Central PMCID: PMC2860852.
2. Wang* M, Topalovski* M, Toombs JE, Wright CM, Moore ZR, Boothman DA, Yanagisawa H, Wang H, Witiewicz A, Castrillon DH, and Brekken RA. Fibulin-5 blocks microenvironmental ROS in pancreatic

cancer. Cancer Research 2015 75:5058-5069. PubMed PMID:26577699; PubMed Central PMCID: PMC4668215.

3. Aguilera KY*, Huang H*, Du W, Hagopian MM, Wang Z, Hinz S, Hwang TH, Wang H, Fleming JB, Castrillon DH, Ren X, Ding K, and Brekken RA. Inhibition of discoidin domain receptor 1 reduces collagen-mediated tumorigenicity in pancreatic ductal adenocarcinoma. Mol. Can. Therapeutics 2017; 16:2473-2485. PMCID: PMC5669827. – cover image
4. Deng J, Kang Y, Cheng CC, Li X, Dai B, Katz MH, Men T, Kim M, Koay EA, Huang H, Brekken RA and Fleming JB. DDR1-induced neutrophil extracellular traps drive pancreatic cancer metastasis. JCI Insight, 2021 6:146133. Doi: 10.1172/jci.insight.146133 PMID: 34237033. PMCID: PMC8492346

V. Tumor microenvironment as a regulator of tumor cell phenotype. We have uncovered multiple pathways through which tumor cell phenotype is regulated. Microenvironmental conditions present in tumors directly contribute to the efficacy of therapy and impact tumor cell behavior. We have discovered that multiple signaling pathways in stromal cells directly affect the biology of tumor cells and can drive or prevent epithelial plasticity.

1. Ludwig KF*, Du W*, Sorrelle NB, Wnuk-Lipinska K, Topalovski M, Toombs JE, Cruz VH, Yabuuchi S, Rajeshkumar NV, Maitra A, Lorens JB and Brekken RA. Axl inhibition enhances chemotherapy and targets immune suppression in pancreatic cancer. Cancer Research 2018 78: 246-255. PMID: 29180468; PMCID PMC5754222.
2. Hosein AN, Huang H, Wang Z, Parmar K, Du W, Huang J, Maitra A, Olson E, Verma U and Brekken RA. Cellular heterogeneity during mouse pancreatic ductal adenocarcinoma progression at single-cell resolution. JCI Insight 2019 5: pii: 129212 PMID: 31335328 PMCID: PMC6777805 https://doi.org/10.1172/jci.insight.129212
3. Du W, Phinney NZ, Huang H, Wang Z, Westcott J, Toombs JE, Zhang Y, Beg MS, Wilkie TM, Lorens JB and Brekken RA. AXL is a key factor for cell plasticity and promotes metastasis in pancreatic cancer. Mol Can Res 2021 19:1412-1421 PMID:33811159 PMCID PMC8349827
4. Zhang* Y, Arner* E, Rizvi A, Toombs JE, Huang H, Warner SL, Foulks JM, and Brekken RA. Axl inhibitor TP-0903 reduces metastasis and therapy resistance in pancreatic cancer. Mol Can Ther. 2022 21: 38-47. PMCID: PMC8742768

Complete List of Published Work in Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/rolf.brekken.1/bibliography/public/

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