General Information

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Education:

1995	M.D., Medicine	Capital University of Medical Science, Beijing, China
2000	Ph.D., Cancer Biology	University of Texas, MD Anderson Cancer Center

Postdoctoral Training:

03/2000-07/2003	*Postdoctoral Fellow*	*Tumor Biology*	Massachusetts General Hosp.

Faculty Academic Appointments:

2003-2007	*Instructor*	Harvard Medical School
2007-present	*Assistant Professor*	Harvard Medical School

Appointment at Hospitals/ Affiliated Institution:

2000-2003	*Research Fellow in Radiation Oncology*	Massachusetts General Hosp.
2003-present	*Assistant Biologist in Radiation Oncology*	Massachusetts General Hosp.

Major Administrative Leadership Positions:

2003-present	*Co-Director of Cellular, Molecular and Histology Core, Steele Laboratory*	Massachusetts General Hosp.

Committee Service:

2006-2009	*Voting Member, Subcommittee on Research Animal Care*	Massachusetts General Hosp.

Professional Societies:

Year	Society	Role
1996-present	*American Association of Cancer Research*	Member

Grant Review Activities:

2009	*RC1 Ad hoc Reviewer*	NIH-NCI

Editorial Activities:

Year	Role	Name of Journal
2000-present	*ad hoc reviewer*	Cancer Research
2000-present	*ad hoc reviewer*	Journal of Clinical Investigation
2000-present	*ad hoc reviewer*	American Journal of Pathology
2002-present	*ad hoc reviewer*	Cancer Cell
2003-present	*ad hoc reviewer*	The Journal of Neuroscience
2000-present	*ad hoc reviewer*	Clinical Cancer Research
2000-present	*ad hoc reviewer*	Proceedings of National Academy of Science

Honors and Prizes:

1995-2000	*R.E. Bob Smith Research Fellowship*	*MD Anderson Cancer Center*
1997 and 1999	*Travel Awards*	*Graduate School of Biomedical Science, University of Texas, Houston*
2005	*Claflin Distinguished Scholar Award*	*Harvard Medical School*
2012	*Clinical Research Award*	*Children's Tumor Foundation*
2013	*Ira Spiro Research Award*	*NIH/NCI Proton Federal Share*
2013	*Drug Discovery Initiative Award*	*Children's Tumor Foundation*

Report of Funded and Unfunded Projects

Funding Information

Past

2005-2007

Claflin Distinguished Scholar Award
Harvard Medical School
Project PI
The role of PDGF-D in human ovarian cancer progression
The major goal of the study is to use human ovarian cancer xenograft to study the role and mechanisms of PDGF-D in ovarian canc er progression.

2008-2009

Federal Share Proton Beam Income Program Grant
National Cancer Institute
Project PI

The role of PlGF in tumor progression after Anti-VEGF therapy
The major goal of the study is to use human ovarian cancer xenograft to study the role and mechanisms of PlGF in ovarian cancer escape from anti-VEGF therapy.

2006-2011

P01

National Cancer Institute
Co-Leader Core B
Integrative Pathophysiology of Solid Tumors
The major goal of this Program Project is to overcome the barriers to drug delivery by the tumor vasculature and establish biomarkers and modify interstitium to improve drug distribution.

2006-2011 R01
National Cancer Institute
Co-Investigator
Role of BMDCs in Tumor Growth and Relapse
The major goal of this R01 is to characterize gene expression, kinetics, phenotype and function of BMDC in a systematic study of their incorporation in growth and treated tumors.

2011-2014 Novel approaches to anti-metastasis therapy in breast cancer
National Cancer Institute
Co-Director Cell, Molecular and Histology Core ($297,583)
The major goal of this project is develop and utilize molecular/cellular techniques to study mechanisms of tumor metastasis.

2012-2015 Strategies for personalized treatment of metastatic breast cancer: vascular normalization and sensitization
US Army Medical Research Grant
Co-Director Cell, Molecular and Histology Core ($4,997,628)
The goal of this grant is to improve antiangiogenic therapy in metastatic breast cancer by optimizing the schedule of therapy, and identifying new targets and biomarkers of response.

2013-2015 A correlative study of angiogenic markers in human brain arteriovenous malformations.
National Cancer Institute/Massachusetts General Hospital
Project PI ($50,000)
The major goal of this grant is to investigate the angiogenic markers in human brain arteriovenous malformations using clinical samples and zebrafish model.

2013-2015 Effect of anti-VEGF and radiation on NF2 Vestibular Schwannoma
Children's Tumor Foundation
Project PI ($150,000)
The major goal of this grant is to investigate whether anti-VEGF therapy can enhance the efficacy of radiation therapy.

2013-2016 Effect of TGF-beta blockade in recurrent NF2 vestibular Schwannoma
Children's Tumor Foundation
Project PI ($50,000)

The major goal of this grant is to investigate whether TGF-beta blockade can enhance the efficacy of radiation therapy and reduce recurrence/relapse after radiation therapy

2016-2017 Combining immunotherapy and antiangiogenic therapy in NF2 schwannoma model
Children's Tumor Foundation
Project PI ($85,000)
The major goal of this grant is to test the optimal schedule and dosing to combine anti-VEGF and immune checkpoint inhibigors.

2016-2017 Combining immune checkpoint blockade and radiation therapy for NF2 vestibular schwannomas
Ira Spiro Translational Research Awards
Project PI ($50,000)
The goal of this grant is to test the therapeutic potential of combined radiation therapy with immune checkpoint inhibitors.

2012-2017 Enhancing chemosensitivity of ovarian cancer with TGF-beta blockade
American Cancer Society
Project PI ($800,000)
The major goal of this grant is to investigate TGF-beta blockade as a novel approach to overcome chemoresistance in ovarian cancer and miR-155 as a novel biomarker for chemosensitivity.

2012-2019 Integrative pathophysiology of solid tumors
National Cancer Institute
Co-Director Cell, Molecular and Histology Core ($720,000)
The major goal of this PPG is to develop molecular/cellular techniques for the study of mechanisms of tumor evades anti-VEGF treatment

Current:

2016-2019 Immunotherapy for NF2 Vestibular Schwannomas
DoD
Project PI ($450,000)
The major goal of this grant is characterize the immune response after anti-VEGF treatment and investigate the therapeutic potential of combined anti-VEGF and immune checkpoint inhibitors.

2018-2020 Reprogramming the tumor microenvironment to enhance anti-tumor immunity in NF2 schwannoma model
Children's Tumor Foundation
Project PI ($85,000)
The major goal of this grant is to test the hypothesis that reprogramming the tumor microenvironment can enhance the efficacy of immunotherapy.

2017-2020 Characterizing the biology of tumor growth and pain response in Schwannomatosis.
MGH Research Fund
Project PI ($100,000)
The major goal of this grant is to characterize the biology and molecular mechanisms that contribute to the tumor growth and pain response in Schwannomatosis patient-derived models.

2016-2020 Normalizing tuberculosis granuloma vasculature and matrix to improve drug delivery and efficacy
Bill and Melnda Gates Foundation Grant
Co-Investigator ($2,000,000)
The major goal of this grant is to normalize the blood vessels and matrix in tuberculosis granulomas to improve the delivery and efficacy of anti-TB drugs.

Report of Local Teaching and Training:

Teaching of Students in Courses:

2002-present Methods in Biomedical Engineering (annual)
Course faculty
Massachusetts General Hospital, HMS
10-30 postdoctoral fellows, graduate students and technologists
3 hours of contact time with learners

Laboratory and Other Research Supervisory and Training Responsibilities:

2001-2003 Co-mentor of graduate research student Pooja Pathak (MIT)/ Steele Laboratory
Daily mentorship for 2 years

2001-2003 Supervisor of molecular research technician Chelsea Swandal, Steele Laboratory
Daily supervision for 2 years

2003-2005 Co-mentor of graduate research student David Cochran (MIT)/Steele Laboratory
Daily mentorship for 2 years

2003-2005 Daily supervision of molecular research technician Melanie Berg, Steele Laboratry, Daily supervision for 1.5 years

2005-2007 Supervisor of molecular research technician Peichun Lin, Steele Laboratory
Daily supervision for 2 years

2008-2010 Supervisor of molecular research technician Dannie Wang, Steele Laboratory
Daily supervision for 2 years

2009-2010 Supervision of summer research student Tony Shi (Cornell University), Steele Laboratory

2011-2012 Supervisor of molecular research technician Lu Wang, Steele Laboratory
Daily supervision for 6 months

2011- Supervision of summer research student from various universities and medical schools, 3 months every year

2013- Supervisor of molecular research technician ShanMin Shin, Steele Laboratory
Daily supervison for 2 year

Formally Supervised Trainees:

2008-2010	JieQiong Liu	Research Fellow, MGH
2010-2012	Wei Chen	Research Fellow, MGH
2012-2013	Xing Gao	Research Fellow, MGH
2012-2013	Chong Liu	Research Fellow, MGH
2012-2014	Yingchao Zhao	Research Fellow, MGH
2013-2015	Yanxia Zhao	Research Fellow, MGH
2012-present	Meenal Datta	PhD student, Tufts University
2015-2016	Na Zhang	Research Fellow, MGH
2015-2016	Jinghong Cao	Research Fellow, MGH
2015-present	Jie Chen	Research Fellow, MGH
2016-present	Zohreh Amoozgar	Research Fellow, MGH
2016-present	Sampurna Chatterjee	Research Fellow, MGH
2016-present	Yanling Zhang	Research Fellow, MGH
2016-present	Limeng Wu	Research Fellow, MGH
2016-present	Jun Ren	Research Fellow, MGH
2017-present	Yao Sun	Research Fellow, MGH

Local Invited Presentations:

2014 "Work-In-Progress Meeting" /Invited seminar speaker
DF/HCC Angiogenesis Invasion and Metastasis (AIM): Children's Hospital Vascular Biology Program, Boston, MA

Report of Regional, National and International Invited Teaching and Presentations:

2013 Effect of combined anti-VEGF and radiation therapy in NF2 vestibular schwannoma. Children's Tumor Foundation Annual Conference/Speaker (abstract)

2014 NF2 State of the Art Conference, Boston, MA/Invited Speaker

2015 Combined anti-VEGF and radiation treatment for NF2 vestibular schwannoma. Children's Tumor Foundation Annual Conference/Speaker

2016 Normalizing the tumour microenvironment to improve drug delivery and efficacy.
Immunotherapy and Resistence to Therapy/Invited Speaker

2016 Targeting placental growth factor/neuropilin 1 pthway inhibits growth and spread of medulloblastoma.
New England Neuro-Oncology/Invited Speaker

2016 Target the tumor microenvironment to overcome resistance.
Boston Angiogenic Meeting/Invited Speaker

2017 Combined cMET blockade and radiation treatment on tumor growth and hearing function.
Children's Tumor Foundation Annual Converence/Invited Speaker

Report of Scholarship:

Publications:

Peer-Reviewed Publications:

1. Xie, K., Wang, Y., Huang, S., Xu, L., Bielenberg, D., Salas, T., McConkey, D.J., Jiang, W., Fidler, I.J. Nitric oxide-mediated apoptosis of K-1735 melanoma cells is associated with down regulation of Bcl-2. Oncogene. 1997; 15(7): 771-9.
2. Xie, K., Bielenberg, D., Huang, S., Xu, L., Salas, T., Juang, S.H., Dong, Z., Fidler, I.J. Abrogation of tumorigenicity and metastasis of murine and human tumor cells by transfection with the murine IFN-beta gene: possible role of nitric oxide. Clinical Cancer Research. 1997; 3(12 Pt 1): 2283-94.
3. Juang, SH., Xie, K., Xu, L., Wang, Y., Yoneda, J., Fidler, I.J. Use of retroviral vectors encoding murine inducible nitric oxide synthase gene to suppress tumorigenicity and cancer metastasis of murine melanoma. Cancer Biotherapy & Radiopharmaceuticals. 1997; 12: 167-75.
4. Xie, K., Wang, YF., Huang, S., Xu, L., Bielengerg, D., Salas, T., McConkey, D.J., Jiang, W., Fidler, I.J. Nitric oxide-mediated apoptosis of K-1735 melanoma cells is associated with down regulation of Bcl-2. Oncogene. 1997; 15:771-9.
5. Juang, SH., Xie, K., Xu, L., Shi,Q., Wang, YF., Yoneda, J., Fidler, I.J. Suppression of tumorigenicity and metastasis of human renal carcinoma cells by infection with retroviral vectors harboring the murine inducible nitric oxide synthase gene. Human Gene Therapy. 1998; 9:845-54.
6. Xu, L., Xie, K., Fidler, I.J. Therapy of human ovarian cancer by transfection with the murine Interferon beta gene: role of macrophage-inducible nitric oxide synthase. Human Gene Therapy. 1998; 9:2699-27-8.
7. Xu L., Xie, K., Mukaida, N., Matsushima, K., Fidler, I.J. Hypoxia-induced elevation in Interleukin-8 expression by human ovarian carcinoma cells**.** Cancer Reseaerch. 1999; 59(22): 5822-9.
8. Xu, L., Fidler, I.J. Acidic pH-induced elevation in Interleukin-8 expression by human ovarian carcinoma cells. Cancer Research. 2000; 60: 4610-6.
9. Xu L. Yoneda J. Herrera C. Wood J. Killion JJ. Fidler IJ. Inhibition of malignant ascites and growth of human ovarian carcinoma by oral administration of a potent inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. International Journal of Oncology. 2000; 16(3): 445-54.
10. Xu, L., Fidler, I.J. Interleukin 8: An autocrine growth factor for human ovarian cancer. Oncology Research. 2000; 12:97-106.
11. Brown, E.B., Campbell, R.B., Tsuzki, Y., Xu, L**.,** Carmeliet, P., Fukumura, D., Jain, R.K. *In vivo* measurement of gene expression, angiogenesis and physiological function in tumors using multiphoton laser scanning microscopy. Nature Medicine. 2001; 7(7): 864-8.
12. Fukumura, D,, Xu, L**.,** Chen, Y., Gohongi, T., Seed, B., Jain, R.K. Hypoxia and acidosis independently up-regulate vascular endothelial growth factor transcription in brain tumors *in vivo*. Cancer Research. 2001; 61(16): 6020-24.

13. Tsuzuki, Y., Carreira, C.M., Xu, L**.,** Jain, R.K., Fukumura, D. Pancreas microenvironment promotes VEGF expression and tumor growth: novel window model for pancreas tumor angiogenesis and microcirculation. Laboratory Investigation. 2001; 81(10): 1439-51.

14. Xu, L., Fukumura, D., Jain, R.K. Acidic extracellular pH induces VEGF in human glioblastoma cells via AP-1 and requires ERK1/2 MAPK. Mechanism of low pH induced VEGF. Journal of Biological Chemistry. 2002; 277 (13): 11368-74.

15. Izumi, Y., Xu, L., di Tomaso, E., Fukumura, D., Jain, R.K. Tumour biology: herceptin acts an anti-angiogenic cocktail. Nature. 2002; 416:279-80.

16. Herrera, C.A., Xu, L**.,** Bucana, C.D., Silva, E.G., Hess, K.R., Gershenson, D.M., Fidler, I.J. Expression of metastasis-related genes in human epithelial ovarian tumors. International Journal of Oncology. 2002; 20(1): 5-13.

17. Bockhorn, M., Tsuzuki, Y., Xu, L., Frilling, A., Broelsch, C.E., Fukumura, D. Differential vascular and transcriptional responses to anti-vascular endothelial growth factor antibody in orthotopic human pancreatic cancer xenografts. Clinical Cancer Research. 2003; 9 (11): 4221-4226.

18. Garkavtsev, I., Kozin, S., Chernova, O., Xu, L., Winkler, F., Brown, E., Barnett, G.H., and Jain, R.K. The candidate tumour suppressor protein ING4 regulates brain tumour growth and angiogenesis. Nature Medicine. 2004; 428(6980): 328-32.

19. Fukumura, D., Ushiyama, A., Duda, D.G., Xu, L., Chatterjee, V.K.K., Garkavtsev, I., Jain, RK. Paracrine regulation of angiogenesis and adipocyte differentiation during adipogenesis *in vivo*. Circulation Research. 2003; 93(9): e88-97.

20. Xu, L., Pathak, P.S., Fukumura, D. Hypoxia-induced activation of p38 MAPK and PI3K signaling pathways contributes to expression of Interleukin-8 in human ovarian carcinoma cells. Mechanism of hypoxia induced Interleukin 8. Clinical Canacer Research. 2004; 10(2): 701-7.

21. Winkler, F., Kozin, S.V., Tong, R.T., Chae, S.S., Booth, M.F., Garkavtsev, I., Xu, L., Hicklin, D. J., Fukumura, D., di Tomaso, E., Munn, L.L., and Jain, R.K. Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. Cancer Cell. 2004; 6(6): 553-63.

22. Xu, L., Tong R., Cochran, D.M., and Jain, R.K. Blocking platelet-derived growth factor-D/platelet-derived growth factor receptor beta signaling inhibits human renal cell carcinoma progression in an orthotopic mouse model. Cancer Research. 2005; 65 (13): 5711-9.

23. Kashiwagi, S., Izumi, Y., Gohongi, T., Demou, Z.N., Xu, L., Huang, P.L., Buerk, D.G., Munn, L.L., Jain, R.K., and Fukumura, D. NO mediates mural cell recruitment and vessel morphogenesis in murine melanomas and tissue-engineered blood vessels. Journal of Clinical Investigation**.** 2005; 115(7): 1816-27.

24. Xu, L., Cochran, D.M., Tong, R.T., Winkler, F., Kashiwagi, S., Jain, R.K., and Fukumura, D. PlGF overexpression inhibits tumor growth, angiogenesis and metastasis by depleting VEGF homodimers in orthotopic mouse models. Cancer Research. 2006; 66(8): 1-7.

25. Hagendoorn, J., Tong R., Fukumura D., Lin Q., Lobo J., Padera T.P., Xu L., Kucherlapati R., Jain R.K. Onset of abnormal blood and lymphatic vessel function and interstitial hypertension in early stages of carcinogenesis. Cancer Research**.** 2006; 66(7): 3360-4.

26. Lawenda, B.D., Smith D.E., Xu, L., Niemierko, A., Silverstein, J.R., Boucher, Y., Kashiwagi, S., Held, K.D., Jain R.K., Loeffler, J.S., Eisenberg D.M., Blumberg. J.B. Do the

dietary supplements epigallocatechin gallate or vitamin e cause a radiomodifying response on tumors in vivo? A pilot study with murine breast carcinoma. Journal of the Society Integrative Oncology. 2007; 5(1): 11-7.

27. Xu, L., Jain, R.K. Downregulation of PlGF by promoter hypermethylation in human lung and colon carcinoma. Molecular Cancer Research. 2007; 5(9): 873-80.
28. Kashiwagi, S., Tsukada, K., Xu, L., Miyazaki, J., Kozin, S.V., Tyrrell, J.A., Sessa, W.C., Gerweck, L.E., Jain, R.K., Fukumura, D. Perivascular nitric oxide gradients normalize tumor vasculare. Nature Medicine. 2008; 14(3): 255-7.
29. Xu, L., Duda, DG., di Tomaso, E., Ancukiewicz, M., Chung, DC., Lauwers, GY., Samuel, R., Shellito, P., Czito, BG., Lin, PC., Poleski, M., Bentley, R., Clark, JW., Willett, CG., Jain, RK. Direct evidence that Bevacizumab, an anti-Vascular Endothelial Growth Factor antibody, upregulates SDF-1a, CXCR4, CXCL6, and Neuropilin 1 in tumors from patients with Rectal cancer. Cancer Research. 2009. 69(20): 7905-10. PMID: 19826039.
30. Gerstner, E.R., Eichler, A.F., Plotkin, S.R., Drappatz, J., Doyle, C.L., Xu, L., Duda, D.G., Wen, P.Y., Jain, R.K. and Batchelor, T.T. Phase I trial with biomarker studies of vatalanib (PTK787) in patients with newly diagnosed glioblastoma treated with enzyme inducing anti-epileptic drugs and standard radiation and temozolomide. J. Neurooncol. 2011. 103(2):325-32. PMID: 20821342.
31. Liao, S., Liu, JQ., Lin, P., Shi, T., Jain, RK., Xu, L. TGF-beta blockade controls ascites by preventing abnormalization of lymphatic vessels in orthotopic human ovarian carcinoma model. *Clinical Cancer Research. 2011. 17(6):1415-24.* PMCID: 21278244.
32. Liu, JQ., Liao, S., Huang, YH., Samuel, R., Shi, T., Naxerova, K., Huang, P., Kamoun, W., Jain, RK., Fukumura, D. and Xu, L. PDGF-D improves drug delivery and efficacy via vascular normalization, but promotes lymphatic metastasis by activating CXCR4 in breast cancer. Clinical Cancer Research. 2011. *17(11):3638-48*. PMCID: 1459800
33. Duda, D.G., Kozin, S.V., Kirkpatrick, N.D., Xu, L., Fukumura, D., Jain, R.K. CXCL12(SDF1a)-CXCR4/CXCR7 pathway inhibition: an emerging sensitizer for anti-cancer therapies? Clinical Cancer Research. 2011. 17(8): 2074-80. PMCID:21349998
34. Goel, S., Duda, D.G., Xu, L., Munn, L.L., Boucher, Y., Fukumura, D., Jain, R.K. Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev. 2011. 91(3): 1071-121. PMID: 21742796.
35. Liu, J. Liao, S. Diop-Frimpong, B., Chen, W., Goel, S., Naxerova, K., Ancukiewicz, M., Boucher, Y., Jain, R.K., Xu, L. TGF-beta blockade improves the distribution and efficacy of therapeutics in breast carcinoma by normalizing the tumor stroma. Proc Natl Acad Sci USA. 2012. 109(41): 16618-23. PMID: 22996328.
36. Snuderl, M., Batista, A., Kirkpatrick, N.D.,de Almodovar, C.R., Riedemann, L., Walsh, E.C., Anolik, R., Huang, Y., Martin, J.D., Kamoun, W., Knevels, E., Schmidt, T., Farrar, C.T., Vakoc, B.J., Mohan, N., Chung, E., Roberge, S., Peterson, T., Bais, C., Zhelyazkova, B.H., Yip, S., Hasselblatt, M., Rossig, C., Niemeyer, E., Ferrara, N., Klagsbrun, M., Duda, D.G., Fukumura, D., Xu, L., Carmeliet, P., and Jain, R.K. Placental growth factor/neuropilin 1 signaling is a therapeutic target in pediatric medulloblastoma. Cell. 2014. 152(5):1065-76. PMID: 23452854.
37. Datta, M., Via, L.E., Kamoun, W.S., Liu, C., Chen, W., Seano, G., Weiner, D.M., Schimel, D., England, K., Martin, J.D., Gao, X., Xu, L., Barry 3rd, C.E., Jain, R.K. Anti-vascular endothelial growth factor treatment normalizes tuberculosis granuloma vasculature and improves small molecule delivery. Porceeds of National Academy of Science 2015. 112 (6):1827-32. PMID: 25624495

38. Datta M, Via LE, Chen W, Baish JW, Xu L, Barry CE 3rd, Jain RK. Mathematical Model of Oxygen Transport in Tuberculosis Granulomas. Ann Biomed Eng. 2015. Aug 8. [Epub ahead of print] PMID: 26253038

39. Gao X, Zhao Y, Stemmer-Rachamimov AO, Liu H, Huang P, Chin S, Selig MK, Plotkin SR, Jain RK, Xu L. Anti-VEGF treatment improves neurological function and augments radiation response in NF2 schwannoma model. Porceeds of National Academy of Science 2015. Nov 24;112(47):14676-81. PMID: 26554010

40. J. Kloepper, L. Riedemann, Z. Amoozgar, G. Seano, K. H. Susek, V. Yu, N. Dalvie, R. L. Amelung, M. Datta, J. W. Song, V. Askoxylakis, J. W. Taylor, C. LuEmerson, A. Batista, N. D. Kirkpatrick, K. Jung, M. Snuderl, A. Muzikansky, K. G. Stubenrauch, O. Krieter, H. Wakimoto, L. Xu, L. L. Munn, D. G. Duda, D. Fukumura, T. T. Batchelor, and R. K. Jain, "Ang2/VEGF bispecific antibody reprograms macrophages and resident microglia to antitumor phenotype and prolongs glioblastoma survival. *Proceedings of the National Academy of Sciences* 2016; 113 (16):4476-81. PMID: 27044098 .

41. T. E. Peterson, N. D. Kirkpatrick, Y. Huang, C. T. Farrar, K. Marijt, J . Kloepper, M. Datta, Z. Amoozgar, G. Seano, K. Jung, W. S. Kamoun, T. Vardam, M. Snuderl, J. Goveia, S. Chatterjee, A. Muzikansky, C. C. Leow, L. Xu, T. T. Batchelor, D. G. Duda, D. Fukumura, and R. K. Jain, "Dual inhibition of Ang2 and VEGF receptors normalizes tumor vasculature and prolongs survival in glioblastoma by altering macrophages. *Proceedings of the National Academy of Sciences* 2016; 113(16):4470-5. PMID: 27044097.

42. Zhao F, Ohgaki H, Xu L, Giangaspero F, Chunde L, Li P, Yang Z, Wang B, Wang X, Wang Z, Ai L, Zhang J, Luo L, Liu P. Molecular subgroups of adult medulloblastoma: a long-term single-institution study. Neuro-Oncology. 2016. 18(7):982-90. PMID:27106407.

43. Askoxylakis V, Badeaux M, Roberge S, Batista A, Kirkpatrick N, Snuderl M, Amoozgar Z, Seano G, Ferraro GB, Chatterjee S, Xu L, Fukumura D, Duda DG, Jain RK. A cerebellar window for intravital imaging of normal and disease states in mice. *Nature Protocol.* 2017;12(11):2251-2262. PMID: 28981123. PMCID: PMC5918134.

44. Zhang N, Gao X, Zhao Y, Datta M, Liu P, Xu L. Rationally combining anti-VEGF therapy with radiation in NF2 schwannoma. *Journal of Rare Disease Research and Treatment.* 2017;1(2):51-55. PMID: 28191549. PMCID: PMC5300073.

45. Zhang N, Chen J, Ferraro G, Wu L, Datta M, Jain RK, Plotkin SR, Stemmer-Rachamimov. A, Xu, L. Anti-VEGF treatment improves neurological function in tumors of the nervous system. *Experimental Neurology* 2017. pii: S0014-4886(17)30236-4. doi: 10.1016/j.expneurol.

46. Zhao Y, Liu P, Zhang N, Chen J, Landegger LD, Wu L, Zhao F, Zhao Y, Zhang J, Fujita T, Stemmer-Rachamimov A, Ferraro GB, Liu H, Muzikansky A, Plotkin SR, Stankovic KM, Jain RK, Xu L. Targeting the cMET pathway augments radiation response without adverse effect on hearing in NF2 schwannoma models. *Proceedings of National Academy of Science. USA*. 2018. 115(9): E2077-E2084.

47. Zhao, Y., Cao, J., Melamed, A., Worley, M., Gockley, A., Jones, D., Nia, H.T., Zhang, Y., Stylianopoulos, T., Kumar, A.S., Mpekris, F., Datta, M., Sun, Y., Wu, L., Gao, X., Yeku, O., del Carmen, M., Spriggs, D.R., Jain, R.K., and Xu, L. Losartan treatment enhances chemotherapy efficacy and reduces ascites in ovarian cancer models by normalizing the tumor stroma. *Proceedings of National Academy of Science USA.* 2019. Pii:201818357. Doi:10.1073/pnas.1818357116. PMID:30659155.

48. Chen J, Landegger LD, Sun Y, Ren J, Maimon N, Wu L, Ng MR, Chen JW, Zhang N, Zhao Y, Gao X, Fujita T, Roberge S, Huang P, Jain RK, Plotkin SR, Stankovic KM, Xu L. A cerebellopontine angle mouse model for the investigation of tumor biology, hearing, and neurological function in NF2-related vestibular schwannoma. *Natature Protocol.* 2019;:ePub - PMID: 30617350 - DOI: 10.1038/s41596-018-0105-7.

Non-peer reviewed scientific or medical publicationsmaterials:

1. Fidler, I.J., Singh, RK., Yoneda, J., Kumar, R., Xu, L**.,** Dong, Z., Bielenberg, DR., McCarty, M., Ellis, LM. Critical determinants of neoplastic angiogenesis. The Cancer Journal 2000; 6 (supl 3): S225-S236.
2. Fidler, IJ., Bielenberg, D.R., Slaton, J., Xu, L., Dinney, CPN., Dong, Z. Interferon-mediated antiangiogenic therapy. Journal of National Cancer Institute 2000; 1092: 4-12.
3. Fidler, I.J., Yoneda, J., Herrera, C., Wood, J., Xu, L. Specific Keynote: Molecular determinants of angiogenesis in ovarian cancer. Gynecologic Oncology 2003; 88: S29-S36.
4. Jain, R.K., Xu, L. alphaPlGF: a new kid on the antiangiogenesis block. Cell. 2007; 131(3):443-5.
5. Xu, L., Czito, BG., Willett, CG. Epigenetic markers in rectal cancer. Clinical Cancer Research. 2010. 16(10):2699-701.
6. Xu ,L., and Liu, P. Future Directions in NF2 research. In: Neurofibromatosis (Editors: Liu P and Xu L). People's Medical Publishing House, co. LTD, Beijing.
7. Zhang ,L., Gao, X., Zhao, Y., Datta, M., Liu, P., Xu, L. Rationally combining anti-VEGF therapy with radiation in NF2 schwannoma. Journal of Rare Diseases Research and Treatment. 2016. 1(2): 51-55.

Narrative Report:

My areas of expertise are 1) the biology of tumor-host interaction, and 2) the development of novel therapeutic targets for cancer. I aim to translate this knowledge into improved therapies by conducting preclinical and clinical studies in collaboration with MGH clinicians. I'm currently leading the following projects:

Reprogramming the tumor microenvironment to enhance immunotherapy in ovarian cancer.

Ovarian cancer is the most lethal of the gynecologic malignancies. Approximately 22,500 new cases of ovarian cancer are diagnosed annually in the U.S., with a mortality of 14,000. Following initial debulking surgery, ovarian cancer patients generally receive a chemotherapy regimen that includes a platinum complex (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel). However, despite initial responsiveness, the majority of patients with advanced ovarian cancer eventually relapse with resistant disease. The use of immune checkpoint blockers (ICBs), such as antibodies against programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has revolutionized therapy of multiple malignancies. However, the use of immune checkpoint blockers (ICBs) has had limited efficacy in patients with ovarian cancer with objective response rates of only 10% to 15%. Therefore, development of alternative therapeutic strategies for ovarian cancer treatment a. high clinical priority. Tumor progression, metastasis and treatment response or resistance are profoundly influence by interactions of cancers with their microenvironment. Tumor microenvironment (TME) consists of nonmalignant cells of the tumor such as cancer associated fibroblasts, endothelial cells and pericytes composing tumor vasculature, immune and inflammatory cells, bone marrow derived cells, and the extracellular matrix. The abundant ECM present in some tumors induces and stores "solid stress" that compresses blood and lymphatic vessels. The consequential reduction in tumor blood perfusion impairs the delivery of drugs (e.g., ICBs) and causes hypoxia. Hypoxic cells are more aggressive and more resistant to radiotherapy and chemotherapeutics that require oxygen to be effective. Hypoxia also contributes to immunosuppression. Our overarching hypothesis is that reprogramming the tumor microenvironment of ovarian cancer will enhance the outcome of immunotherapy.

Development of new adjunct therapies in NF2 vestibular schwannoma

Over the past few decades, radiation therapy has become a standard treatment for vestibular schwannoma. For patients with sporadic vestibular schwannomas, radiation therapy is associated with long-term tumor control rates exceeding 95%. However, hearing preservation rates after radiation therapy range from 50% to 80%. Thus, hearing loss is the main limitation of radiation therapy for vestibular schwannoma and identifying options that minimize hearing loss are urgently needed. Clinical trial of Anti-VEGF treatment in patients with NF2 vestibular schwannoma patients showed that it inhibited tumor progression and improved hearing. However, not all NF2 patients with hearing loss respond to bevacizumab monotherapy, and for the patients whose hearing improved, the response is transient. Furthermore, some patients are unable to tolerate long-term bevacizumab treatment. Based on these, we proposed to develop new adjunct therapies to radiation and bevacizumab treatment. First, we study the effect of combining radiation with VEGF inhibition for treatment of NF2-related schwannoma. The results of this study will determine the rationale for combining anti-VEGF treatment and radiation therapy in humans and for the timing of radiation therapy relative to bevacizumab treatment. In addition, the study will provide critical information on biomarkers for the normalization window that may be used in human studies to guide dosing and assess efficacy and toxicity. In parallel, we are studying the effect of targeting the TGF-beta and HGF/cMet pathway in combination with anti-VEGF or radiation therapy in vestibular schwannoma.

Characterizing the biology of tumor progression and pain response in Schwannomatosis patient-derived models.

Schwannomatosis is a form of neurofibromatosis characterized by the growth of multiple benign Schwann cell tumors, called schwannomas. The unique hallmark of Schwannomatosis that distinguishes it from other forms of neurofibromatosis is intractable, debilitating pain in a large percentage of patients. Most Schwannomatosis patients who experience pain do not find relief in existing medications or procedures to combat pain. Because there are limited cell lines and no preclinical models with which to study the disease, the etiology of pain in Schwannomatosis is not clear. Thus, developing a platform to study the biology of Schwannomatosis and identify strategies that relieve pain in patients with Schwannomatosis is a significant unmet need. Malignant cancer cells can grow indefinitely in cell culture and can form xenograft tumors in mice, which allows for the characterization of their growth and assessment of novel therapeutic drugs. However, as a benign tumor, Schwannomatosis tissues isolated from patients do not grow in culture. Therefore, we developed a platform using 3D culture to study tumor-induced pain and identify novel strategies that relieve pain in patients with Schwannomatosis. The successful completion of this study will lead to a major leap forward in our understanding of Schwannomatosis-induced pain and in the availability of tools that can be used to develop novel, efficacious therapies to treat Schwannomatosis pain.

Improve the tuberculosis treatment efficacy by modulating the granuloma microenvironment

Anti-VEGF treatment are widely studied and tested in the oncology field, however, whether it can be applied to infectious disease is not known. We studied granulomas lesions from human tuberculosis patients and rabbit models, we found that blood vessels in TB granulomas are very similar to tumor blood vessels in that they are collapsed and structurally abnormal, lacking pericyte coverage of the endothelial layer. This functional abnormality lead to increased hypoxia and may hinder drug delivery. Further more, we applied anti-VEGF treatment to rabbit TB model and are examine its effect on drug delivery and efficacy.