The Faculty of Medicine of Harvard University

Curriculum Vitae

Name:	**Lei Xu**
Office Address:	**Massachusetts General Hospital (MGH)** **55 Fruit Street, Cox-7** **Boston, MA, 02114**
Work Phone:	**617-726-8051**
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Education:

MD	Medicine		Capital University of Medical Science Beijing, China
PhD	Cancer Biology Thesis advisor:	Isaiah J. Fidler	University of Texas, MD Anderson Cancer Center Houston, TX

Postdoctoral Training:

Postdoctoral Fellow	Tumor Biology Mentor: Rakesh K. Jain	Massachusetts General Hospital Boston, MA

Faculty Academic Appointments:

Instructor	Radiation Oncology	Massachusetts General Hospital
Assistant Professor	Radiation Oncology	Massachusetts General Hospital
Associate Professor	Radiation Oncology	Massachusetts General Hospital

Professional Societies

American Association of Cancer Research	Active member
Society of Immunotherapy of Cancer	Member
American Association for the Advancement of Science	Member
Microcirculatory Society	Member

Honors and Prizes:

R.E. Bob Smith Research Fellowship	MD Anderson Cancer Center	Outstanding research in cancer research
Claflin Distinguished Scholar Award	Harvard Medical School	Outstanding research in tumor biology

Report of Funded Projects

Current

2022 - 2024	Profile losartan-induced changes in tumor microenvironment and inflammation in NF2 VS patient samples. Children's Tumor Foundation Clinical Research Award PI - ($150,000) The major goal of this grant is to investigate in NF2 patient samples of the changes induced by losartan treatment.
2022 - 2026	Screening trial for pain relief in Schwannomatosis (STARFISH). Department of Defense Clinical Trial Award Co-PI - Project PI, Plotkin, Scott ($1,204,851) The major goal of this grant is to study the analgesic effect of erenumab-aooe, an FDA-approved CGRP receptor inhibitor, in SWN patients with moderate-to-severe pain.
2022 - 2027	Co-targeting IL-6 and EGFR signaling for the treatment of Schwannomatosis and associated pain. NIH-NINDS R01 PI - ($2,386,445) The goal of this grant is to investigate the biology of tumor-induced pain response and develop novel therapeutic strategies to simultaneously control tumor growth and tumor-associated pain in Schwannomatosis models.
2023 - 2024	Targeting the Ang II signaling to uncouple the efficacy and toxicity of immunotherapy in NF2. MGH Executive Committee on Research (ECOR) Interim Support Grant PI ($90,000) This study aims to investigate the efficacy of losartan in enhancing the efficacy and limiting the toxicity of immunotherapy in NF2 mouse models.
2023 - 2024	Developing a thrombopoietin inhibitor to treat NF2 hearing loss and schwannoma growth. Children's Tumor Foundation Drug Discovery Initiative Award Co-PI - Project PI, Sherman, Lawrence ($85,000) The goal of this grant is to test novel thrombopoietin inhibitors in modulating the tumor microenvironment, tumor progression and hearing loss in vestibular schwannoma models.
2023 - 2028	Targeting HMGB1 to improve hearing and enhance therapy for NF2 Vestibular Schwannomas. NIH-NIDCD R01 PI - ($2,874,318) The goal of this grant is to investigate the treatment efficacy and mechanisms of blocking HMGB1 in preserving hearing function and controlling tumor growth.
2024-2026	Targeting the HIF2 signaling pathway to improve hearing and enhance therapy for NF2 vestibular Schwannomas. Children’s Tumor Foundation PI - ($200,000) The goal of this grant is to investigate the treatment efficacy and mechanisms of blocking HIF2 in preserving hearing function and controlling tumor growth.

2024 - 2026	Reprogramming the tumor microenvironment to enhance immunotherapy in ovarian cancer. American Cancer Society Mission Boost Award PI - ($600,000) The major goal of this grant is to investigate the effect of modulating the tumor microenvironment on enhancing treatment efficacy in ovarian cancer models.

Training Grants and Mentored Trainee Grants

2023 - 2025	Co-Targeting HMGB1 and EGF signaling for the treatment of NF2 and associated hearing loss. Children's Tumor Foundation Young Investigator Award Mentor to Zhenzhen Yin, post-doctoral fellow The goal of the study is to test combinatory strategy to preserve hearing function in NF2 models.
2023 - 2025	To understand the role of apelin mediated angiogenesis in NF2 associated tumors. Children's Tumor Foundation Young Investigator Award Co-Mentor to Srirupa Bhattacharyya, post-doctoral fellow The goal of the study is to study the functional role of apelin in tumor angiogenesis in NF2 models.
2024 - 2027	Co-Targeting HMGB1 and EGF signaling for the treatment of NF2 and associated hearing loss. American Cancer Society Post-Doctoral Award Mentor to Zhenzhen Yin, post-doctoral fellow The goal of the study is to test combinatory strategy to preserve hearing function in NF2 models.

Report of Clinical Activities and Innovations

Clinical Innovations:

Clinical development of losartan for hearing preservation in patients with NF2. (2021 – Present)	I discovered that blocking angiotensin signaling using losartan preserves hearing function in the NF2 mouse model. Based on our findings, the Department of Radiation Oncology at MGH has amended the current ongoing clinical trial (NCT01199978), to include 10 patients to be treated with losartan concurrently with fractionated proton therapy, with follow-up evaluations for hearing function.
Identification of biomarkers in autism patients. (2021 – Present)	We have identified biomarkers in patients with autism spectrum disorder treated with probiotic and oxytocin combination therapy. This work report the finding of clinical trial (NCT03337035).
Clinical development of screening trial for pain relief in Schwannomatosis. (2023 – Present)	I am the co-PI on clinical trial NCT05684692. I established preclinical models to study mechanisms of tumor-induced pain response and to screen for potential treatment targets. Based on the encouraging initial results, in collaboration with Dr. Scott Plotkin, we initiated the clinical trial testing the analgesic effect of erenumab-aooe, an FDA-approved CGRP receptor inhibitor, in SWN patients with moderate-to-severe pain. I'll be leading the mechanistic and biomarker studies in the trial.

Report of Technological and Other Scientific Innovations

Use of signal transduction inhibitors and combination therapies for the prevention or treatment of cancer and angiogenesis related diseases. US Patent US-20060036086-A1 (2006)	As a member of the Steele Laboratories for Tumor Biology, my colleagues and I identified and demonstrated the use of signal transduction inhibitors and combination therapies for the prevention or treatment of cancer and angiogenesis-related diseases. The use of these agents has since been used/validated by multiple labs in the US and abroad.

Report of Scholarship

Peer-Reviewed Scholarship in print or other media:

Research Investigations

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. PMID:9266963
2. 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. PMID:9266963
3. 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: 2283-94. PMID:9815626
4. 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. PMID:10851463
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. PMID:9581907
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. PMID:9874268
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 Research***. 1999; 59(22): 5822-9. PMID:10582705
8. 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. PMID: 10874492
9. **Xu, L**., Fidler, I.J. Interleukin 8: An autocrine growth factor for human ovarian cancer. ***Oncology Research***. 2000; 12:97-106. PMID:11132928
10. **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. PMID:10675474

11. **Xu, L**., Fidler, I.J. Acidic pH-induced elevation in Interleukin-8 expression by human ovarian carcinoma cells. ***Cancer Research***. 2000; 60: 4610-6. PMID 10969814

12. 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

13. 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. PMID:11433354

14. 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. PMID:11598156

15. 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. PMID:11507045

16. **Xu, L**., Fukumura, D., Jain, R.K. Acidic extracellular pH induces VEGF in human glioblastoma cells via AP-1 and requires ERK1/2 MAPK. ***Journal of Biological Chemistry***. 2002; 277 (13): 11368-74. PMID:11741977

17. 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. PMID: 11907566

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19. 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. PMID:12586082

20. 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. PMID:14525808

21. 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. PMID:14519649

22. 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. PMID:15029197

23. 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

24. **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. ***Clinical Canacer Research***. 2004; 10(2): 701-7. PMID:14760093

25. **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. PMID:15607960. *Corresponding author.

26. 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. PMID:15951843

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31. 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. PMID:18278052

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33. **Xu, L.*,** Czito, BG., Willett, CG. Epigenetic markers in rectal cancer. ***Clinical Cancer Research***. 2010. 16(10):2699-701. PMID: 24060492. *Corresponding author.

34. 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. Neuro-Oncology***. 2011. 103(2):325-32. PMID: 20821342

35. 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.* PMID: 21278244.

    Figure from the paper featured as journal cover.

36. 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*. PMID: 21459800

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38. 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. ***Proceedings of National Academy of Science USA.*** 2012. 109(41): 16618-23. PMID: 22996328

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44. 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**. Munn, L. 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 National Academy of Science USA.*** 2016; 113 (16):4476-81. PMID: 27044098

45. 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, **Xu, L**. 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 National Academy of Science USA.*** 2016; 113(16):4470-5. PMID: 27044097

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    Figure from the paper featured as an online rotator for the journal, and the study is featured on HMS and DoD website.

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disorder: a randomized double-blinded placebo-controlled pilot trial. ***Nutrients.*** 2021, 13(5): 1522. PMID: 32082606

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