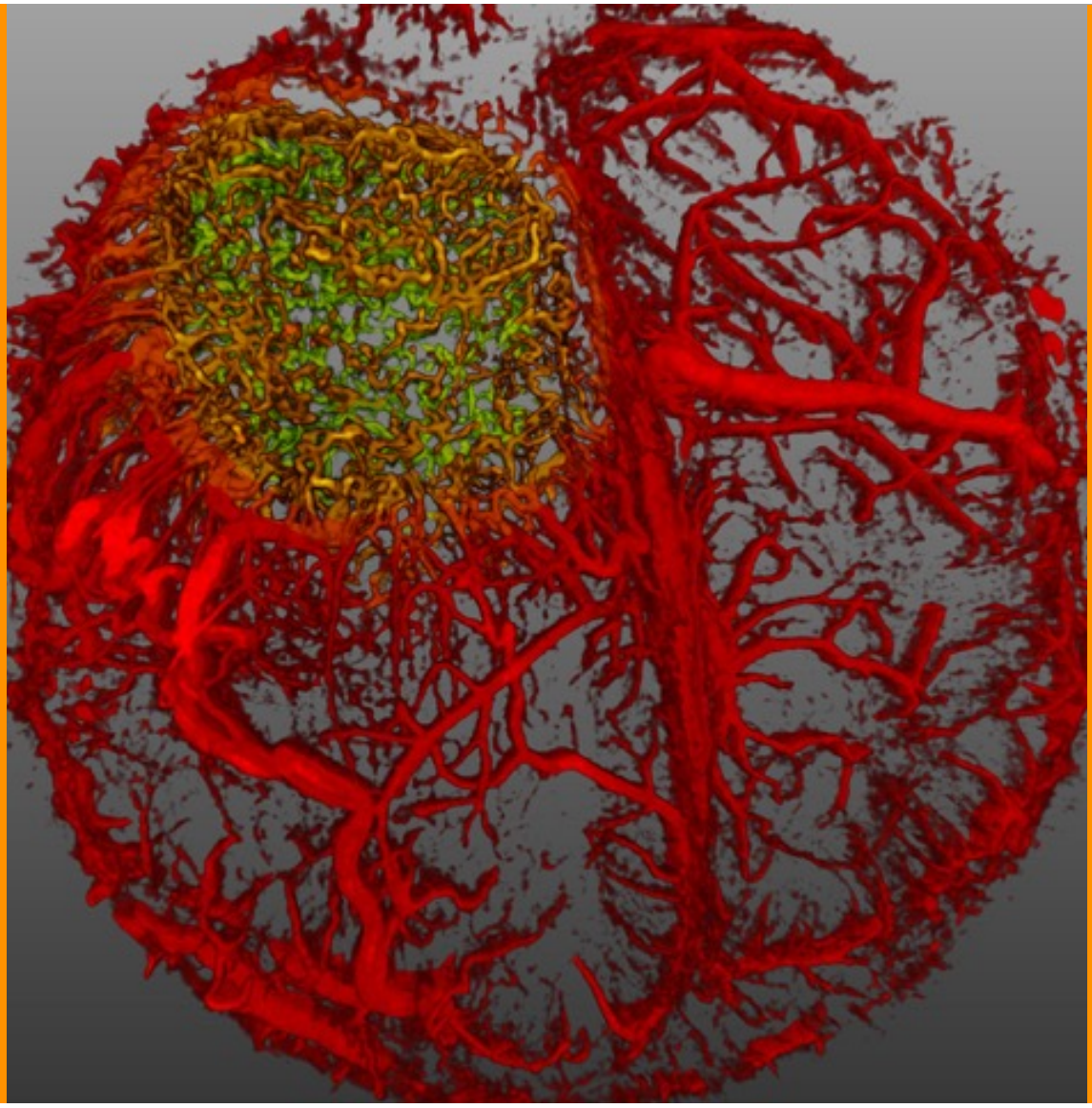
EDWIN L. STEELE LABORATORIES

DEPARTMENT OF RADIATION ONCOLOGY
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL



RESEARCH REPORT 2016

Dr. Jain received the US Medal of Science, May 19, 2016 ***"for pioneering research at the interface of engineering and oncology, including tumor microenvironment, drug delivery, and imaging; and for discovering groundbreaking principles guiding the development and novel use of drugs for cancer and non-cancerous diseases."***

Alumni celabration, June 25, 2016

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PREFACE

A solid tumor is an organ composed of cancer cells and host stromal cells—nourished by blood vessels and drained by lymphatic vessels—all embedded in an extracellular matrix. The interaction among these cells, the surrounding matrix, and the local cellular microenvironment influences the expression of various genes, whose protein products control the pathophysiological characteristics of the tumor, govern tumor progression and affect the tumor's response to various therapies. The overarching goal of our research is to dissect the role of tumor microenvironment in tumor progression and treatment resistance, and to translate this knowledge into improved cancer detection, prevention and treatment in humans. A tight integration between bench and bedside and application of engineering principles to oncology is a hallmark of our research.

To unravel the complex biology of tumors, the Steele Laboratories have developed an array of optical technologies, mathematical models and sophisticated animal preparations. These include multiphoton microscopy and genetically engineered mice with surgically implanted transparent windows, which together permit the real-time visualization of gene expression and function in tumors and their surrounding host stroma. This undertaking has provided unprecedented molecular, cellular, anatomical and functional insights into the vascular, interstitial and cellular barriers to cancer treatment. Specifically, we demonstrated that the blood and lymphatic vasculature, fibroblasts, immune cells and the extracellular matrix associated with tumors are abnormal, which collaborate together to create a hostile tumor microenvironment characterized by hypoxia, low pH and high interstitial fluid pressure.

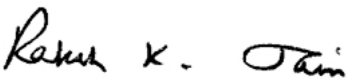
We next hypothesized that agents that induce "normalization" of the microenvironment should improve the treatment outcome. Our work in this area has come to fruition and led to two novel strategies: vascular normalization and matrix normalization. The Steele Laboratories are now recognized worldwide for the discovery that direct and indirect antiangiogenic therapies can "normalize" tumor vessels, thus improving blood perfusion, oxygenation and treatment efficacy in cancer patients. This revolutionary concept explained how bevacizumab (Avastin®)—the first antiangiogenic drug to receive FDA approval—works in patients and has spawned a number of basic and clinical studies. The vascular normalization hypothesis also explained how bevacizumab and other anti-VEGF drugs improve vision in patients with wet age-related macular degeneration and opened doors to treating other non-malignant diseases harboring abnormal vasculature that afflict more than 500 million people worldwide. These include neurofibromatosis-2 (NF2), tuberculosis and cardiovascular atherosclerotic plaque rupture. In 2014, our clinical findings showing the reversal of hearing loss in NF2 patients by normalizing their blood vessels led to the approval of bevacizumab for these patients in UK.

In parallel, by imaging collagen and measuring perfusion in tumors in vivo, we discovered that the extracellular matrix compresses blood vessels and impedes drug delivery in desmoplastic tumors (e.g., pancreatic cancer, hepatocellular carcinoma, certain breast cancers). We subsequently discovered that widely prescribed angiotensin blockers to control hypertension are capable of "normalizing" the extracellular matrix, opening compressed tumor vessels and improving the delivery and efficacy of therapy. This finding offers new hope for improving treatment of highly fibrotic tumors, and led to a phase II clinical trial in 2013 at MGH on testing the benfit of adding losartan to the standard of care (chemotherapy and radiation followed by surgery) in patients with locally advanced pancreatic ductal adenocarcinoma (NCT01821729). Preliminary findings from this trial – presented at the ASCO GI meeting on January 20, 2017 – are very positive and support testing our hypothesis in randomized trials in pancreatic cancer patients. If successful, this will represent a major paradigm shift in the treatment of this uniformly fatal disease and open doors for improving treatment of other malignant and non-malignant diseases.

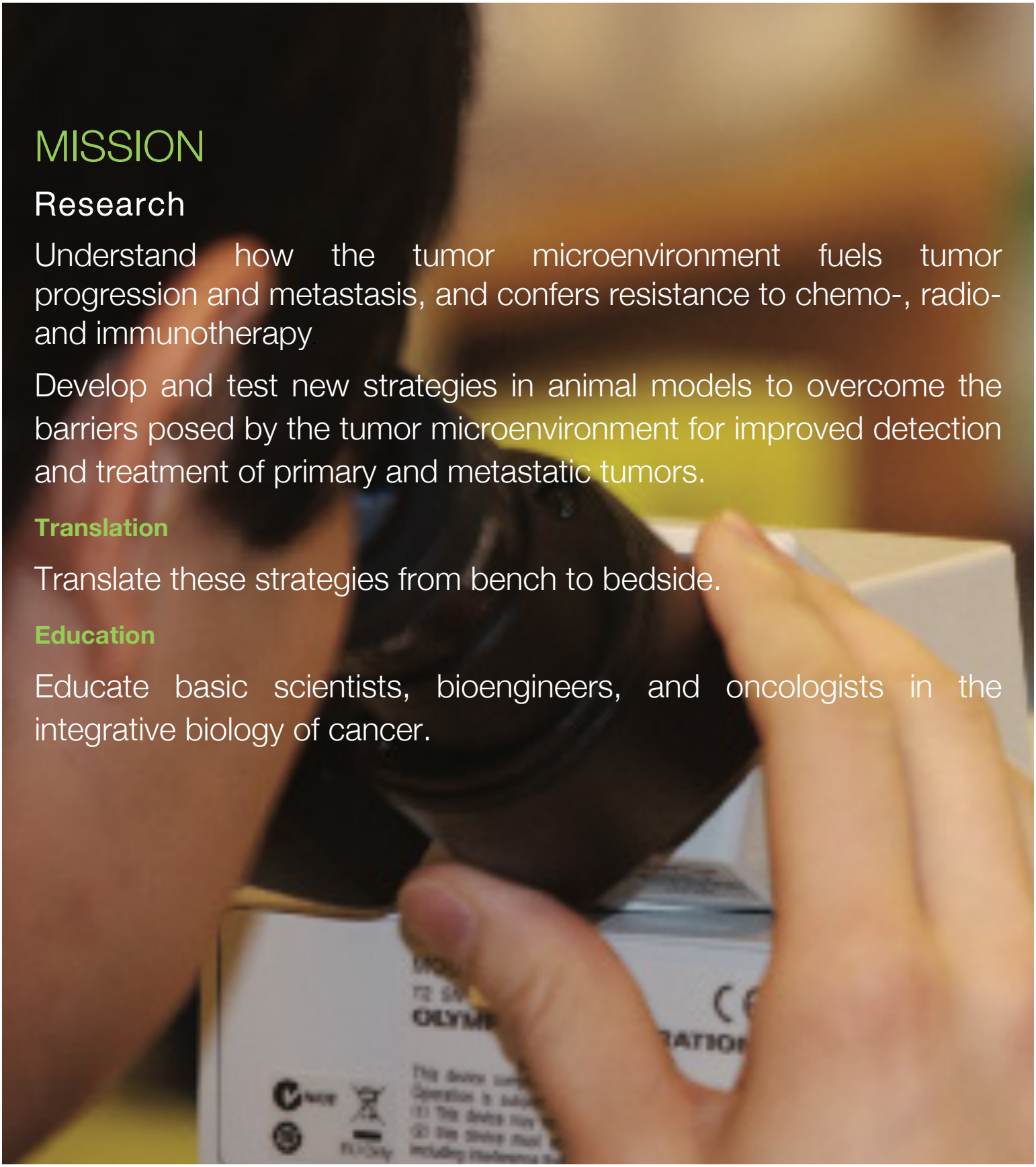
The Edwin L. Steele Laboratories for Tumor Biology were founded in 1975 by a generous gift by Mrs. Jane Bancroft Cook in memory of her late husband Edwin L. Steele. In addition, she endowed the Andrew Werk Cook Professorship of Radiation Oncology at Harvard University/MGH in honor of her second husband. Andrew Werk Cook. These donations to cancer research at MGH

have been critical in the growth of tumor biology research at MGH, which over the years has led to improved understanding and treatment of cancer. The continued support of Ms. Elizabeth Steele (daughter of Mrs. Cook) and Jane's Trust has allowed these discoveries to continue. In September 1991, Dr. Rakesh Jain was recruited to be the director of the Steele Laboratories, starting with a small team of six people. We have since grown to approximately 65 members. The Steele Labs have fostered the careers of the 9 current faculty members, who collectively have trained over 200 students and fellows. We have developed a leading, multidisciplinary research and education program in the integrative biology of cancer. In addition to the research within our laboratory, we have a number of collaborative projects with clinicians and scientists at the MGH and other medical research centers worldwide. Results from the Steele Laboratories, as well as those from these collaborations, have been reported in more than 500 publications, and have been presented at national and international meetings. In recognition of our past research accomplishments and future research plans, members of the research group have received more than 75 awards, including membership in all three branches of the US National Academies – Medicine, Engineering and Sciences, US Medal of Science and more than 100 grants from various private and government agencies including the Alex's Lemonade Stand Foundation, the American Association for Cancer Research, Brain Tumor Society, American Cancer Society, Burroughs Welcome Fund, Cancer Research Institute, the Charles A. King Trust, Children's Tumor Foundation, Damon Runyon Foundation, Fat Disorders Research Society, Fund for Medical Discovery, the Bill and Melinda Gates Foundation, German Cancer Foundation, Goldhirsch Foundation, Humboldt Foundation, Jane's Trust Foundation, Lymphatic Education and Research Network, Lustgarten Foundation, the National Institutes of Health, the National Foundation for Cancer Research, the National Science Foundation, Susan Komen Foundation, United Negro College Fund, U.S. Army Breast Cancer Program, Yvonne Silverman Bequest and the Whitaker Foundation. We are especially grateful to Mr. Dilip Shanghvi and Sun Pharma Advanced Research Corporation (SPARC) for their generous support of our research in 2016.

The Steele Laboratories are also dedicated to education, offering a bi-annual course in tumor pathophysiology to Harvard-MIT students. Annually, we also offer a continuing medical education course at Harvard Medical School on tumor microenvironment (immunology, angiogenesis and metastasis) for national and international students, with the 32nd offering scheduled for September 5 – 8.



Rakesh K. Jain, Ph.D.
Andrew Werk Cook Professor of Radiation Oncology
(Tumor Biology)
Director, E.L. Steele Laboratories



MISSION

Research

Understand how the tumor microenvironment fuels tumor progression and metastasis, and confers resistance to chemo-, radio- and immunotherapy

Develop and test new strategies in animal models to overcome the barriers posed by the tumor microenvironment for improved detection and treatment of primary and metastatic tumors.

Translation

Translate these strategies from bench to bedside.

Education

Educate basic scientists, bioengineers, and oncologists in the integrative biology of cancer.

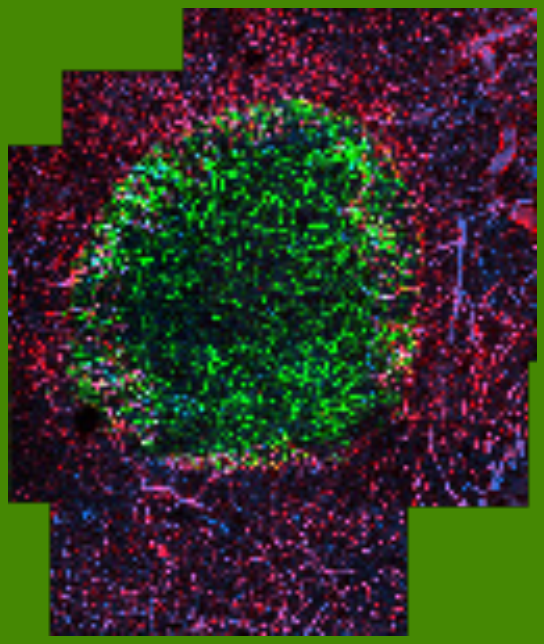
STRATEGIES

Research

- Unravel causal relationships between genetic and physiological function in various micro-environments using in vitro and in vivo microscopy and image analysis.
- Analyze experimentally and mathematically the physical and physiological barriers and pharmacokinetics, and integrate the resulting information.
- Overcome barriers by creative manipulation of the tumor microenvironment.
- Emphasize multidisciplinary approaches, integration of engineering with tumor biology, and bench-to-bedside translation.

Education

- Develop and implement integrative tumor biology and bioengineering courses.
- Provide close mentorship by the faculty on individual research projects.



ACCOMPLISHMENTS

- Recruited and sustained a “critical” number of outstanding faculty, post-doctoral fellows, graduate students and technical staff to support core research.
- Initiated and continued collaborations with members of Massachusetts General Hospital, Harvard, MIT and other institutions.
- Established state-of-the-art intravital microscopy facilities.
- Developed unique in vivo tumor models.
- Published over 650 original and review articles in peer-reviewed journals and books in seven core research areas: Angiogenesis and blood flow, Tumor microenvironment, Transvascular transport, Interstitial and lymphatic transport, Cell mechanics and transport, Mathematical modeling, and Bench-to-bedside translation.
- Obtained research support from the National Cancer Institute and other government and private sources.
- Received more than 100 awards from various scientific societies and academic institutions.
- Developed innovative courses in the integrative biology of cancer.
- Translated laboratory findings to cancer patients: e.g., the first treatment of schwannomas by bevacizumab and completion of more than two dozen multi-disciplinary clinical trials of anti-angiogenic therapy on cancer patients with brain, colorectal, liver, ovarian and connective tissue.
- Proposed the vascular normalization hypothesis that has changed the thinking in the field of oncology about how targeted therapies work.

RESEARCH GRANTS AND AWARDS

1976-1999	National Science Foundation
1980-	National Institute of Health – Jain; Munn (2000 -); Fukumura (2002-); Boucher (2003-); Padera (2009-); Duda (2009-); Garkavtsev (2013-)
1980-	American Cancer Society – Jain; Burton (2000 - 2001); di Tomaso (2001-2003); Brown (2003-2004); Xu (2012-2016)
1991-	Humboldt Fellowships - Leunig, Dellian, Sckell
1992-	National Research Service Awards - Berk, Munn, Litchtenbeld, Kadambi, Ramanujan, Koenig, Brown, Luong
1992	Kurt Wohl Lecturer (U. Delaware) - Jain
1992-1996	Howard Hughes Fellowship - Gazit, Ang
1992-1993	Hybritech-Lilly
1993-2000	Outstanding Investigator Grant, National Cancer Institute – Jain
1993, 1994	Instrumentation Awards, American Microcirculation Society - Berk, Leunig, Yuan, Jain
1994-1996	DuPont-Merck
1994-1996	Enzon
1994-2012	Deutsche Forschungsgemeinschaft - Patan, Hansen-Algenstaedt, Gralla, Kunert
1994	Outstanding Alumnus Award, Indian Institute of Technology – Jain
1995	Whitaker Award, Biomedical Engineering Society – Jain
1996-2002	US Army Breast Cancer Program
1996-2000	Whitaker Foundation (Munn)
1996-1999	Whitaker Junior Faculty Award - Berk, Munn
1996	Landis Award, Microcirculatory Society - Jain
1996-1998	Whitaker BERE Fellowship - Fukumura
1997-	National Science Foundation Fellowship – Padera, Lin, Pathak, Tong
1998-	National Foundation for Cancer Research
1999-2000	Stewart Trust Award – Fukumura
1999	Kaplan Lecture (HMS), Berkeley Lecture (UCB) – Jain
2000	Pharmaceutical and Bioengineering Award, American Institute of Chemical Engineers – Jain
2000-2001	Human Science Foundation Fellowship –Izumi
2000-	Japanese Ministry of Health and Welfare Fellowship – Izumi, Kohno
2000-2001	Japanese Science and Technology Agency Fellowship – Ushiyama
2000-2002	Mildred-Scheel-Stiftung Deutsche Krebshilfe Fellowship – Bockhorn
2000-2001	Genentech
2000-2001	Miravant
2000-2001	ImClone

2000-2001	Whitaker Health Sciences Fund Fellowship – Padera
2000-2003	Biotechnology Training Program Fellow – McKee
2001-2002	Susan Komen Foundation Fellowship – Dolmans
2001-2003	University of Copenhagen Fellowship – Junker
2001-2003	Whitaker Foundation Graduate Fellowship – Cochran
2001	Honorary Fellow, Indian Institute of Chemical Engineers – Jain
2001-	Whitaker Foundation Graduate Fellowship – Tam
2001	Netherlands America Commission for Educational Exchange Fulbright Fellowship – Hagendoorn
2001-2003	Claflin Distinguished Scholar – Xu
2001-2003	University of Tsukuba, Ministry of Education Science and Culture of Japan - Koike
2001-2003	Foundation for Science and Technology of Portugal – Sousa
2002	Bioengineering Division Award of the American Institute for Chemical Engineers –Jain
2002-2006	The Goldhirsh Foundation
2002	Gerritsen Award, Microcirculatory Society – Jain
2002- 2005	Cancer Research Institute – Duda
2002-	Whitaker Foundation Graduate Fellowship – Mok
2003	Alumni Wall of Fame, University of Delaware - Jain
2003-2005	Emmy-Noether grant of the German Research Foundation – Winkler
2003-2005	Susan Komen Foundation Fellowship – Tong
2003-2008	NIH Research Career Development Award – Munn
2003	Institute of Medicine, the National Academy of Sciences – Jain
2003-2005	American Association for Cancer Research Career Development Award – Duda
2003-2005	Japan Society for the Promotion of Science – Nagano
2004	National Academy of Engineering, the National Academy of Sciences – Jain
2004	Robert Bras Lecturer, Princess Margaret Hospital and National Cancer Institute of Canada – Jain
2004-2005	National Defense Medical College Fellowship – Miyazaki
2005-2008	Damon Runyon Foundation Fellowship – Lahdenranta
2005	John S. Laughlin Lecturer, Memorial Sloan-Kettering Cancer Center, New York – Jain
2005	AstraZeneca
2005	French Medical Research Foundation Fellowship-LaCorre

2005	Academic Scientist of the Year, 2005 Pharmaceutical Achievement Awards – Jain
2006-2008	Brain Tumor Society
2006-2008	Claflin Distinguished Award – di Tomaso
2006	Ford Foundation Diversity Fellowship – Dawson
2006-2009	Susan Komen Fellowship – Lacorre
2006-2009	Department of Defense Pre-doctoral Award – Lanning
2005-2008	Department of Defense Pre-doctoral Award – Pieters
2006	Distinguished Service Award, Nature Biotechnology - Miami Symposium on Angiogenesis – Jain
2006	Outstanding Achievement Award, Society of American Asian Scientists in Cancer Research – Jain
2006	Robert L. Krigel Lecture, Fox Chase Cancer Center, Philadelphia – Jain
2006	Alpha Chi Sigma Research Award, American Institute of Chemical Engineers – Jain
2006	Benjamin Zweifach Distinguished Lecture, The City College, New York – Jain
2007	Research Team Award, Clinical Research Day, MGH – Jain, di Tomaso, Duda, Kozak
2007	Uehara Memorial Foundation Fellowship – Yamashita
2007	Sam Gerson Leadership Chair of Research, Brain Tumor Society – Jain
2007	Drug Discovery Initiative Award, Children's Tumor Foundation – di Tomaso
2008	Sir Godfrey Hounsfield Lecture, Imperial College, London – Jain
2008	Richard D. Frisbee III Oncology Lecture, Yale University–Jain
2008	Sir Godfrey Hounsfield Lecture, Imperial College, London – Jain
2008	Peter C. Reilly Lecture, University of Notre Dame, Indiana–Jain
2008	Charles G. Moertel Lecture, Mayo Clinic, Rochester, Minnesota – Jain
2008	Ashland Distinguished Lecture, University of Kentucky, Lexington, Kentucky–Jain
2008	William E. Schiesser Lecture, Lehigh University, Bethlehem, Pennsylvania – Jain
2008	American Academy of Arts and Sciences–Jain
2008	Spiro Translational Research Award - Duda
2008	Susan Komen Fellowship - Kamoun
2008	Federal Share (Boucher)
2008	Tosteson Postdoctoral Fellowship Award from the Massachusetts Biomedical Research Corporation-Liao
2008	NIH Pathway to Independence Award-Padera
2009	National Academy of Sciences–Jain
2009	Dyax
2009	Zweifach Lecture, UCSD - Jain
2009	Susan Komen Fellowship - Stylianopoulos
2009	Merck Fellowship (Sodunke)
2009	Ruckenstein Lecture, University at Buffalo NY-Jain
2010	DoD Innovator Award (Jain)
2010	Pirkey Lecture, University of Texas at Austin - Jain
2010	Kelley Lectures, Purdue University - Jain
2010	William B. Lowrie Lecture, Ohio State Univ. - Jain
2010	Wagner Lecture, University of Michigan - Jain
2010	Spiro Translational Research Award - Duda
2010	Martin Research Prize for Excellence in Clinical Research-Padera, Tyrrell, Jain, di Tomaso
2011-	Federal Share (Boucher, Fukumura, Duda, Jain, Garkavtsev, Huang, Munn, Xu,)
2011	Gates Foundation
2011	MedImmune (SRA)
2011	Roche (SRA)
2011	NIH Director's New Innovator Award-Padera
2011	Charles A. King Trust Fellowship Award-Liao
2011	Roland T. Lakey Award, Wayne State University - Jain
2011	American Cancer Society Basic Science Lecture, Society of Surgical Oncology - Jain
2011	Rous-Whipple Award, American Society of Investigative Pathology - Jain
2011	Irving O. Shoichet Lecture, University of Toronto, Canada – Jain
2011	Distinguished Research Lecturer, Carnegie Mellon- Jain
2012	NIH Pathway to Independence Award-Liao
2012	One of the 18 Indians Doing Cutting-Edge Research, Forbes (India) -Jain
2012	Herman Schwan Lecture, University of Pennsylvania-Jain
2012	ASCO Science of Oncology Award and Lecture, American Society of Clinical Oncology-Jain
2013	M. Gerritsen Award, Microcirculation Society - Fukumura, Duda, Munn, Jain
2013	Max Kade Foundation-Reiberger
2013	Children's Tumor Foundation-Xu
2013	AACR-Boucher
2014	M. Gerritsen Award, Microcirculation Society - Fukumura, Duda, Munn, Jain
2014	Earl Bakken Distinguished Lecture, Amer. Institute for Medical and Biological Engineering -Jain
2014	AACR-Princess Takamatsu Lecture/Award, American Association for Cancer Research -Jain
2014	One of 50 Oncology Luminaries, American Society of Clinical Oncology (ASCO) -Jain
2014	Most cited paper (2013), Annals of Biomedical Engineering –Jain

2014	Fellow, American Association for the Advancement of Science (AAAS) -Jain
2015	NIH R01 - Munn, Padera, Jain
2015	Rice University Distinguished Alumnus Award –Munn
2015	Secretary General, IASGO –Duda
2015	"Eugene M. Landis Award" The Microcirculatory Society - Fukumura
2015	Honorary Doctorate, Katholieke Universiteit Leuven, Belgium –Jain
2015	Honorary Doctorate, Indian Institute of Technology (IIT), Kanpur, India -Jain
2015	Honorary Doctorate, Duke University -Jain
2015	Capussotti Award (International Association of Surgeons, Gastroenterologists, and Oncologists) –Duda
2015	Honoree of the One Hundred, Mass General Cancer Center –Duda
2015	Foreign Fellow, Indian National Science Academy (INSA) –Jain
2015	LE&RN/FDRS Lipedema Postdoctoral Fellowship -Bouta
2015	Schrodinger Fellowship by the Austrian Science Funds –Pinter
2015	Herman-Holtheusen Award of the German Societyfor Radiation Oncology -Askoxylakis
2015	Humboldt Foundation Feodor Lynen Research Fellowship –Schanne
2015	Susan G. Komen Foundation Postdoctoral Grant; FSQ Fellowship; FMD ECOR -Ferraro
2015	Tufts Graduate School of Arts and Sciences Travel Award, School of Engineering Travel Award, AACR Scholar in Training Award - Datta
2015	Poster of Distinction Award at MGH ECOR SAC Meeting -Ferraro, Datta
2015	De Beaumont Bonelli Foundation Travel Award, Lorini Foundation Award -Seano
2015	ABTA Fellowship -Chatterjee
2015	AACR-Aflac, Incorporated Scholar in Training Award, Keystone Global Helath Award -Jung
2015	Award of the State Scholarship Fund by the China Scholarship Council (CSC) -Y. Zhao
2015	Spiro Award -Padera, Xu
2015	Merrimack Pharma SRA -Duda
2015	Warshaw Award -Fukumura, Duda
2015	Nikon Small World Competition, 5th place-Seano
2015	SPARC SRA - Garkavstev
2015	North America Vascular Biology Organization Outstanding Poster Award- Bazou
2015	Pierre Gilles de Gennes Fondation pour la Recherche Fellowship, Consejo Superior de Investigaciones Cientificas Award-Bazou
2015	Children's Tumor Foundation Drug Discovery Award -Xu
2015	NIH Outstanding Investigator Award -Jain
2015	Bill and Melinda Gates Foundation Grand Challenges: New Interventions in Global Health Award -Jain
2015	Ludwig Institute Grant -Jain
2015	Bayer, BMS SRA -Duda
2015	Rice University Distinguished Alumnus Award –Munn
2016	Inductee, American Institute of Medical and Biological Engineeering -Munn
2016	Heroes of Hope Award Granara-Skerry Trust for Pancreatic Cancer Research - Duda
2016	Won Partners in Excellence Award - Roberge
2016	DoD New Investigator Award – Xu
2016	2016 AACR-GYRIG Scholar-in-Training Award - Jung
2014, 14, 16	One of the top 1% cited researchers in Clinical Medicine, Thomson Reuters -Jain
2016	Princess Takamatsu Cancer Research Fund International Lecturer, Japan -Jain
2016	One of the Most Influential/Cited Authors on the 75th Anniversary of Cancer Research -Jain
2016	R. B. Trull Lecture, University of Texas, Austin-Jain
2016	United States National Medal of Science (for 2013) -Jain
2016	NIH F31 Fellowship – Datta
2016	AACR Postdoctoral Fellowship - Wong
2016	Tosteson Postdoctoral Fellowship - Nia
2016	Uehara Foundation Postdoctoral Fellowship - Shigeta
2016	NIH R01 – Padera, Munn
2016	Feodor-Lynen Postdoctoral Research Fellow - Ghosh
2016	The Kyoto University Foundation - Kawaguchi
2016	Resource Center for Health Science (RECHS) - Kawaguchi

RESEARCH GOALS

The long-term goal of our research is to reveal the role of host-tumor interactions in the biology and therapeutic response of tumors and to translate this insight into improved cancer detection, prevention and treatment. A quantitative understanding of pathophysiology of solid tumors is developed using five unique yet complementary approaches in our research

1 a microscopic approach to directly visualize gene expression, physiological function and delivery of therapeutics *in vivo*.

2 a macroscopic approach using tissue-isolated tumors to access and monitor arterial and venous blood in rodent and human tumors.

3 in vitro characterization of deformability, permeability, migration, adhesion and force generation in cells

4 molecular biology techniques as well as the development of transgenic cell lines and animals

5 mathematical modeling to integrate existing data and to guide new clinical and experimental studies.

These five approaches are intertwined in seven multi-disciplinary projects

1. tumor angiogenesis and blood flow
2. metabolic microenvironment
3. transvascular transport
4. interstitial and lymphatic transport
5. cell mechanics and transport;
6. mathematical modeling
7. translation of laboratory findings to the clinic

Vascular cast of human colon tumor vessels used to study vascular abnormalities. The plastic material was injected and polymerized after the surgical resection of a tumor from the colon of a patient.

The goals of the first project are to understand the molecular and physical mechanisms underlying the temporal and spatial heterogeneities in tumor vasculature; and to develop strategies for manipulating these parameters to "normalize" the tumor vasculature.

The goals of the second project are to determine molecular and cellular mechanisms that lead to the abnormal tumor microenvironment and to develop strategies to "normalize" the microenvironment.

The goals of the third project are to characterize transvascular transport pathways in tumors, to identify molecular mechanisms that govern transport of molecules across the vessel wall, and to develop molecular and physiological strategies for improved transport.

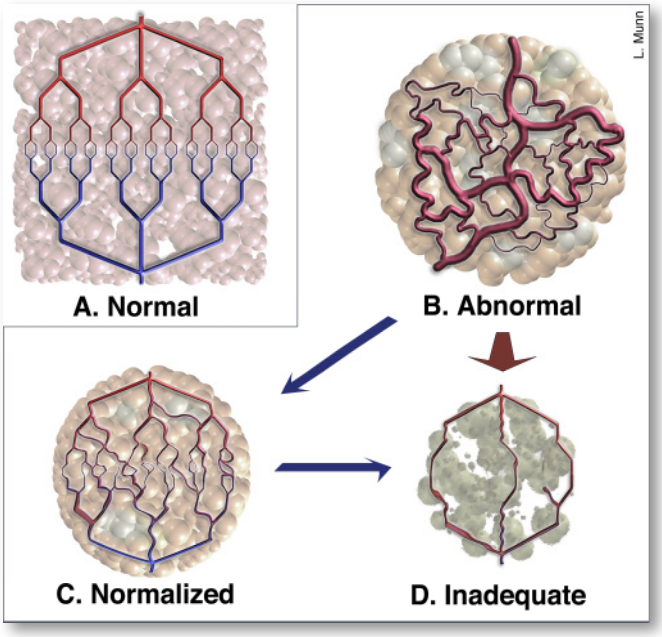
The goals of the fourth project are to characterize transport in the interstitium and relate it to the interstitial structure, to determine the causes of interstitial hypertension, to develop strategies to alter pressure in solid tumors, and to examine the diagnostic and prognostic value of tumor interstitial pressure in the management of cancer. Since lack of functioning lymphatics is a major cause of interstitial hypertension, a related goal is to further our understanding of lymph transport, and to identify inhibitors of lymphangiogenesis and lymphatic function in tumors.

The goals of the fifth project are to quantify the structural rigidity, force generation, and motility of cancer cells and of various lymphocyte subpopulations, to measure the adhesive interactions among lymphocytes, endothelial cells and tumor cells, to define the mechanisms which control these structural and functional properties, to relate these biophysical parameters with the in vivo movement of lymphocytes and cancer cells and to develop novel technologies for separating rare cells from blood based on this understanding.

The goal of the sixth project is to bring together the knowledge generated in the first five projects by developing appropriate mathematical models. Current efforts are focused on improving the delivery of therapeutic agents to tumors using various approaches, scale-up of rodent data to humans, fractal analysis of vascular networks, mathematical modeling of angiogenesis and leukocyte-endothelial interactions and development of new transport and growth equations for solid tumors based.

The goal of the seventh project is to translate our laboratory findings in the clinic with the goal of improving current therapies and to develop new molecular and cellular biomarkers for individualizing cancer treatment.

We believe that our work will continue to provide valuable insight into tumor pathophysiology and suggest novel strategies for improved detection, prevention and treatment of solid tumors.

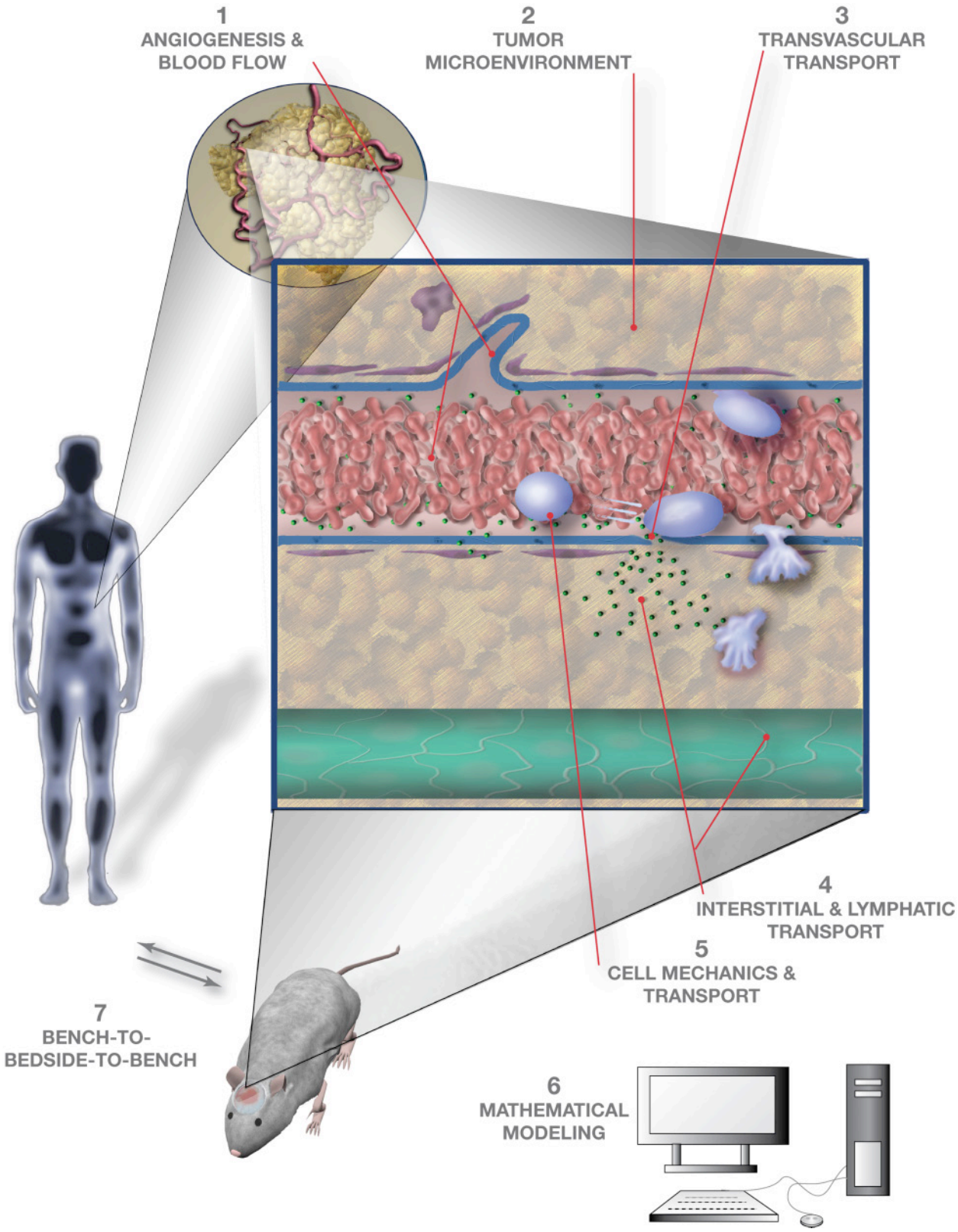


Normalization hypothesis: Anti-angiogenesis drugs cause abnormal tumor vessels (B) to become more normal with better function (C), allowing uniform drug delivery and more effective radiation therapy.

RESEARCH HIGHLIGHTS

Project 1 Angiogenesis and Blood Flow

- Developed sophisticated animal models for studies of tumor angiogenesis, microcirculation, progression, metastases and treatments including dorsal window (Leunig et al., 1992b, Leunig et al., 1995, Leunig et al., 1997), cranial window (Yuan et al., 1994b), liver ((Fukumura et al., 1997b), gallbladder (Gohongi et al., 1999), pancreas (Tsuzuki et al., 2001), mammary fat pad (Monsky et al., 2002), tissue-isolated tumor (Kristjansen et al., 1994, Kristjansen et al., 1996).
- Developed state of the art imaging techniques for in vivo studies including multiphoton laser-scanning microscopy (Brown et al., 2001; Padera et al, 2002), Quantum dots (Stroh et al., 2005; Allen et al, 2010; Liu et al., 2010; Chen et al., 2013), Life time imaging (Kumar et al., 2009), OFDI (Vakoc et al, 2009), (Kim et al., 2010), (Kamoun et al., 2010), video-rate MPLSM (Kirkpatrick et al., 2012),
- Developed a noninvasive model to visualize angiogenesis and adipogenesis and found provocative reciprocal regulation between them, suggesting a novel therapy for obesity related diseases including cancer (Fukumura et al., 2003; Tam et al., 2009b). Established a physiologically based mathematical model to study body weight balance (Tam et al., 2009a).
- Provided the first quantitative measurements of geometric resistance to blood flow and of branching patterns in the rat and human tumor vasculature (Less et al., 1991).
- Established and tested a network model to explain the effect of vasoactive agents on tumor blood flow and interstitial fluid pressure (Zlotecki et al., 1995).
- Developed a novel scheme to quantify the vascular architecture in a tumor (Gazit et al., 1995, Gazit et al., 1997). This analysis has allowed us to calculate the role of vascular heterogeneity in nutrient and drug delivery of tumors (Baish et al., 1997, 2011, Baish and Jain, 2000, 2001).
- Utilized tissue-isolated tumors for residence time distribution studies to examine the accuracy of models used to estimate blood flow (Eskey et al., 1994) and for drug uptake studies to investigate barriers to drug delivery (Kristjansen et al., 1996, Heijn et al., 1999).
- Discovered new mechanisms of tumor angiogenesis (Patan et al., 1996) and vascular anastomosis (Cheng et al., 2011).
- Discovered a new mechanism of intermittent blood flow in tumors (Netti et al., 1996, 2001).
- Demonstrated roles of nitric oxide (Fukumura and Jain, 1998; Fukumura et al., 2006) on the regulation of tumor blood flow (Kristensen et al., 1997; Fukumura et al., 1997a), angiogenesis (Fukumura et al., 2001) and pericyte recruitment (Kashiwagi et al., 2005), and that perivascular nitric oxide gradients normalize tumor vasculature (Kashiwagi et al., 2008) and Tie-2 activation potentiate it (Goel et al., 2013).
- Measured the stress generated by tumor growth to explain vascular collapse (Helmlinger et al., 1997b; Koike et al., 2002) and showed that relieving stress by inducing tumor cell apoptosis could open vessels (Griffon-Etienne et al., 1999; Padera et al., 2004).
- Demonstrated the importance of host organ in tumor angiogenesis, microcirculation (Fukumura et al., 1997b; Tsuzuki et al., 2001; Monsky et al., 2002) and VEGF/bFGF induced vessels (Dellian et al., 1996a), suppression of secondary angiogenesis (Sckell et al., 1998, Gohongi et al., 1999; Hartford et al., 2000) and response to anti-VEGF and HER2 therapies (Bockhorn et al., 2003; Kodack et al., 2012).
- Discovered that tumor induces VEGF-promoter activity in the host fibroblasts (Fukumura et al., 1998), these activated fibroblasts play an active role in angiogenesis (Brown et al., 2001) and the host cells contribute significantly to VEGF production (Tsuzuki et al., 2000) and compensate tumor cells' production (Izumi et al., 2002)
- Discovered indirect pro-/anti-angiogenic effects such as hormone therapy/withdrawal (Jain et al., 1998a; Kristensen et al., 1999b) on blood flow and microcirculation in tumors angiogenesis. Anti-HER2 therapies (Izumi et al., 2002; Kodack et al., 2012)
- Demonstrated that VEGF produced by endothelial cells in oxygen gradients can lead to vascular network formation in vitro (Helmlinger et al., 2000).
- Quantified the frequency of mosaic vessels in tumors (Chang et al., 2000).
- Demonstrated that anti-VEGF and anti -VEGF-R2 antibodies potentiate radiation-induced short term and long term tumor control (Lee et al., 2000; Kozin et al., 2001).
- Demonstrated that decorin inhibits angiogenesis in vitro (Davies et al., 2001).
- Proposed that judiciously applied anti-angiogenic therapy can normalize tumor vasculature (Jain, 2001).
- Discovered the mechanism of blood flow shutdown by PDT (Dolmans et al., 2002a,b).
- Demonstrated that VEGF blockade can retard the growth of spontaneous autochthonus tumors (Izumi et al., 2003).
- Created long-lasting blood vessels in vivo using endothelial cells and mesenchymal precursor cells (Koike et al., 2004), hES cells (Wang et al., 2007), EPCs (Au et al., 2008a), MSCs (Au et al., 2008b), human iPS cells (Samuel et al., 2013).
- Discovered the differential transplantability of tumor stromal cells and stromal cell metastasis (Duda et al., 2004, 2010).
- Demonstrated normalization of tumor vasculature by an anti-angiogenic therapy (Tong et al., 2004; Winkler et al., 2004; Kashiwagi et al., 2008; Kamoun et al., 2009; Huang et al., 2012)
- Characterized nanoparticle transport (Stroh et al., 2005) and the effect of size (Popović et al., 2010; Chauhan et al., 2012), charge (Campbell et al., 2002; Stylianopoulos et al., 2010 & 2013; Han et al., 2013), shape (Chauhan e al., 2011), multistage system (Wong et al., 2011), and vascular normalization (Chauhan et al., 2012)
- Discovered Ang-2 as a potential target for anti-VEGF therapy reistance (Chae et al., 2010).
- Demonstrated that CXCR4 promotes metastasis via Gr-1+ BMDC recruitment (Hiratsuka et al., 2011a).
- Discovered that tumors prime metastatic "soil" by inducing focal hyperpermeability in the lungs (Hiratsuka et al., 2011b).
- Determined how fluid forces and VEGF cooperate to control angiogenic sprouting (Song & Munn, 2011)
- Discovered PlGF/NRP1 as a novel therapeutic target in pediatric medulloblastoma (Snuderl et al., 2013)


1
ANGIOGENESIS &
BLOOD FLOW
2
TUMOR
MICROENVIRONMENT
3
TRANSVASCULAR
TRANSPORT
4
INTERSTITIAL & LYMPHATIC
TRANSPORT
5
CELL MECHANICS &
TRANSPORT
6
MATHEMATICAL
MODELING
7
BENCH-TO-
BEDSIDE-TO-BENCH

RESEARCH HIGHLIGHTS

Project 2 Tumor Microenvironment

- Adapted and developed fluorescence ratio imaging microscopy (FRIM) to measure pH in vivo in normal and tumor microcirculation in the rabbit ear chamber and mouse dorsal chamber (Martin and Jain, 1993, Martin and Jain, 1994, Dellian et al., 1996b).
- Provided the first combined measurement of pH and pO2 profiles in human tumor xenografts (Helmlinger et al., 1997a).
- Demonstrated that VEGF produced by endothelial cells in oxygen gradients can lead to vascular network formation in vitro via an autocrine mechanism (Helmlinger et al., 2000).
- Measured oxygen consumption of endothelial cells in vitro (Helmlinger et al., 2000) and of tumors during various treatments (Hansen-Algenstaedt et al., 2000).
- Delineated the mechanisms of low pH in tumors (Helmlinger et al., 2002).
- Measured glucose metabolism and vascular parameters in lung cancer patients using PET and MRI (Hunter et al., 1998).
- Measured the effect of creatine and cyclocreatine on energy levels in tumors (Kristensen et al., 1999a).
- Determined increase in tumor pO2 by modified hemoglobins (Nozue et al., 1996).
- Examined the feasibility of the Eppendorf histograph for pO2 measurements (Nozue et al., 1997a, Nozue et al., 1997b).
- Demonstrated a lack of universal correlation between pO2 and IFP (Boucher et al., 1995).
- Discovered that HIF1α deletion leads to lower VEGF expression, angiogenesis and oxygenation, yet the tumors grow more rapidly (Carmeliet et al., 1998), and H1F1α (-/-) cells localize in hypoxic regions (Brown et al, 2001).
- Discovered that low pH and pO2 independently regulate VEGF (Fukumura et al, 2001), and delineated the signaling pathways for low pH induced VEGF upregulation (Xu et al., 2002).
- Demonstrated signaling pathways in hypoxia-induced IL-8 expression (Xu et al., 2004).
- Demonstrated that HIF-2α acts as a tumor suppressor (Acker et al., 2005).
- Discovered that the judicious application of anti-angiogenic therapy alleviates hypoxia in tumors (Winkler et al, 2004).
- Developed "smart" nano-particles that become smaller in size once they enter the tumor microenvironment and penetrate deeper into tumors (Wong et al, 2011)
- Discovered that medulloblastoma cells stimulate stromal granule cells via Shh to produce PlGF, which promotes medulloblastoma cell growth and spread (Snuderl et al., 2013)
- Discovered that reprogramming liver tumor microenvironment using CXCR4 inhibition can facilitate immunotherapy (Chen et al, 2015)

Project 3 Transvascular Transport

- Found that decompressing vessels with angiotensin inhibition can enhance oxygen delivery to tumors (Chauhan et al., 2013)
- Provided the first measurement of microvascular permeability in a human tumor xenograft using intravital fluorescence microscopy (Yuan et al., 1993).
- Demonstrated that the local microenvironment of tumors can control permeability (Yuan et al., 1994b; Fukumura et al., 1997b).
- Showed that anti-VEGF antibody or hormone withdrawal can lower tumor permeability and lead to vascular regression (Yuan et al., 1996, Jain et al., 1998a, Lichtenbeld et al., 1999, Jain et al., 1998), yet VEGF showed no correlation with vascular permeability in different sites (Fukumura et al., 1997b).
- Measured the molecular weight and charge dependencies of vascular permeability (Yuan et al., 1994a, 1995; Dellian et al., 2000; Campbell et al., 2002) and discovered that the pore size cut-off for transvascular pathways depends on tumor-host interaction and changes in response to therapy (Hobbs et al., 1998).
- Discovered that hyperpermeability of tumor vessels coupled with high interstitial pressure can lead to vascular stasis (Netti et al., 1996, Baish et al., 1997).
- Measured the hydraulic conductivity (Sevick and Jain, 1991a) and distribution of water channel protein (AQP1) in tumors (Endo et al., 1999).
- Discovered that increase in vascular permeability by VEGF depends on the host-origin of endothelium (Chang et al., 2000) and host-tumor interaction (Monsky et al., 1999).
- Demonstrated that the gaps between endothelial cells cause hyperpermeability in tumors (Hashizume et al., 2000).
- Measured the effect of PlGF and VEGF on the hydraulic conductivity of endothelium in vitro (Dull et al, 2001).
- Demonstrated induction of vascular permeability by nitric oxide in tumors and VEGF-induced angiogenic vessels (Fukumura et al., 1997a and 2001).
- Demonstrated that anti-VEGFR2 antibody reduces vascular permeability and normalizes tumor vasculature (Tong et al., 2004; Winkler et al., 2004).
- Examined how focal vessel hyperpermeability can influence network flow patterns (Sun et al., 2008).
- Found that modulating nanoparticle shape can enhance the penetration of tumors (Chauhan et al., 2011)
- Determined that vascular normalization can enhance the penetration of small but not large nanomedicines in tumors (Chauhan et al., 2012)
- Discovered that inhibiting VE-PTP, which itself inhibits the vessel maturation activities of Tie-2, matures vessels in primary and metastatic lesions to prevent disease progression and enhance radiation sensitivity (Goel et al., 2013)

RESEARCH HIGHLIGHTS

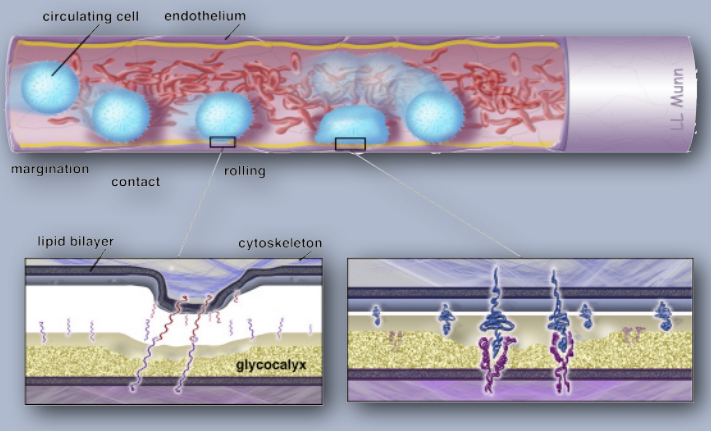
Project 4 Interstitial and Lymphatic Transport

- Provided evidence that microvascular pressure is the principal driving force for interstitial hypertension in tumors (Boucher et al., 1992, Zlotecki et al., 1993, 1995), and that interstitial pressure goes up with the onset of angiogenesis (Boucher et al., 1996).
- Theoretically predicted and experimentally confirmed the time constants of transvascular and interstitial fluid exchange in tumors (Netti et al., 1995) and developed a novel strategy for improving drug delivery based on these findings (Netti et al., 1999).
- Demonstrated that it is possible to lower tumor pressure using nicotinamide (Lee et al., 1992), dexamethasone (Kristjansen et al., 1993), pentoxifylline (Lee et al., 1994a), hemodilution (Lee et al., 1994b), TNFα (Kristensen et al., 1996, Kristensen et al., 1997), taxanes (Griffon-Etienne et al., 1999), radiation (Znati et al., 1996) and various vasoactive agents (Zlotecki et al., 1995).
- Suggested the possibility that pressure could be used as a prognostic marker (Leunig et al., 1992a, Leunig et al., 1994a).
- Demonstrated a lack of universal correlation between pO2 and IFP (Boucher et al., 1995).
- Adapted fluorescence recovery after photobleaching (FRAP) to thick samples (Beck et al., 1993) and used it to measure the effect of charge, molecular weight and configuration on diffusion in gels (Johnson et al., 1995, Johnson et al., 1996a, Johnson et al., 1996b, Pluen et al., 1999).
- Measured the hydraulic conductivity of the tumor interstitial matrix (Boucher et al., 1998).
- Discovered that collagen network contributes to resistance (Netti et al., 2000; Davies et al., 2002; Ramanujan et al., 2002), and to host-organ dependence of interstitial transport in tumors (Pluen, et al, 2001).
- Adapted FRAP to measure binding kinetics between antibody and tumor associated antigens in vitro (Kaufman et al., 1991, Kaufman et al., 1992a, Kaufman et al., 1992b) and in vivo (Berk et al., 1997).
- Demonstrated that VEGF-C, the first lymphangiogenic molecule, leads to lymphatic hyperplasia in skin (Jeltsch et al., 1997), in the tumor margin (Padera et al, 2002), and angiogenesis in tumors (Kadambi et al, 2001).
- Developed a new model for lymphatic transport (Leu et al., 1994) and measured flow velocities in lymph capillaries of the tail skin of mice using RTD and FRAP (Swartz et al., 1996, Berk et al., 1996).
- Provided the first measurements of oncotic pressure in tumors (Stohrer et al, 2000).
- Demonstrated the absence of functional lymphatics in tumors despite the presence of VEGF-C and its receptors (Leu et al., 2000; Padera et al., 2002).
- Demonstrated that LYVE-1 is not specific to lymphatics, and LYVE-1 Prox1 structures, presumably lymphatics are absent in primary and secondary tumors in livers of patients (Mouta-Carreira, et al, 2001)
- Developed a new model for acute lymphedema in the tail and alleviated edema using a flap transfer (Slavin et al., 1999, Losken et al, 2001).
- Developed a technique for optically imaging collagen in tumors in vivo using second harmonic generation (Brown et al., 2003).
- Quantified the dynamics of collagen modification after pharmacologic intervention and provided mechanistic insight into improved diffusive transport induced by the hormone relaxin (Brown et al., 2003).
- Demonstrated that radiation enhances the production of collagen I and reduces fluid flow in tumors (Znati et al., 2003).
- Developed a two-photon correlation microscopy technique and found two-phase nature of interstitial transport in tumors (Alexandrakis et al., 2004).
- Demonstrated that compressive mechanical forces generated by proliferating cancer cells can cause the collapse of intratumor blood and lymphatic vessels (Padera et al., 2004).
- Demonstrated that VEGF-C overexpression leads to the formation of lymphatic vessels that demonstrate retrograde flow and implies that the VEGF-C alone can not produce mature, functional lymphatic vessels (Isaka et al., 2004).
- Demonstrated that nitric oxide and eNOS act on the collecting lymphatic vessels, but not the initial lymphatic vessels, of the mouse tail and alters the rate of lymph flow in these vessels (Hagendoorn et al., 2004).
- Demonstrated that VEGF signaling blockade reduces the tumor interstitial fluid pressure in experimental tumors (Lee et al., 2000; Tong et al., 2004).
- Evaluated tadpole model as a novel system to study lymphangiogenesis (Ny et al., 2005)
- Discovered elevated IFP and abnormal lymphatics in premalignant lesions (Hagendoorn et al., 2006).
- Imaged each step in the process of lymphatic metastasis and found that VEGF-C increases cancer cell arrival in the lymph node and thereby increases metastasis formation (Hoshida et al., 2006).
- Demonstrated a lack of efficacy of VEGFR TKIs against lymphatic metastasis in the adjuvant setting (Padera et al., 2008)
- Demonstrated the critical function of NO in the autonomous contraction of collecting lymphatic vessels (Liao et al., 2011).
- Discovered that the widely-prescribed anti-hypertensive drugs can "normalize" the collagen matrix and improve the delivery and efficacy of drugs in desmoplastic tumors (Diop-Frimpong et al, 2011).
- Found that TGF-beta inhibition can enhance the penetration and efficacy of nanomedicines in tumors (Liu et al., 2012)
- Discovered that VEGF-C sensitizes lymphatic endothelial cells to radiation (Kesler et al., 2014)
- Found that lymph node metastasis do not require sprouting angiogenesis in order to grow (Jeong, Jones et al., 2015).
- Developed mathematical model to characterize the role of mechanobiological inputs in driving lymphatic pumping (Kunert et al., 2015).
- Demonstrated the first dynamic lymph flow measurement without injected contrast in vivo (Blatter et al., 2016).

RESEARCH HIGHLIGHTS

Project 5 Cell Mechanics and Transport

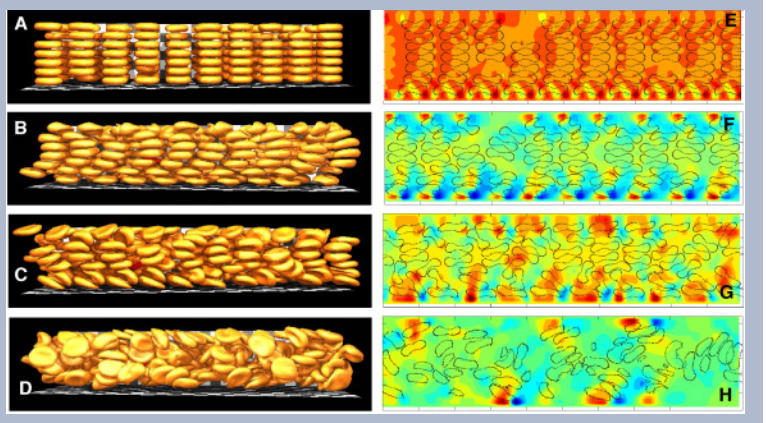
- Adapted and further developed rectangular and cylindrical systems to quantify deformation, rolling and adhesion of lymphocytes (Munn et al., 1994, Yuan et al., 2000).
- Developed a new technology to measure membrane-associated antigen in intact cell monolayers (Munn et al., 1995).
- Demonstrated that interleukin-2 (IL-2) increases the rigidity of NK cells (Melder and Jain, 1992) and that thioglycollate can reduce the rigidity of IL-2 activated NK cells without affecting their cytotoxicity or adhesiveness (Melder and Jain, 1994), and thus avoid entrapment in the lungs (Melder et al, 2001)
- Discovered that RBCs augment selectin and integrin mediated rolling and adhesion of lymphocytes to the vascular endothelium both in vitro and in vivo (Melder et al., 1995b, Munn et al., 1996, Melder et al., 2000; Yuan et al., 2001).
- Demonstrated that rolling in the dorsal skin is reduced but not eliminated in P-selectin deficient mice (Yamada et al., 1995a), and that rolling increases with age (Yamada et al., 1995b).
- Discovered that rolling is normal but adhesion is reduced in E-selectin Mice (Milstone et al., 1998).
- Demonstrated using three different in vivo tumor models that IL-2 activated NK cells preferentially adhere to the tumor vasculature (Ohkubo et al., 1991, Sasaki et al., 1991, Melder et al., 1993, Melder et al., 1994, Melder et al., 1995a), even though the leukocyte-endothelial interaction in tumors is heterogeneous (Fukumura et al., 1995) and differs among subpopulations of lymphocytes (Melder et al., 1997, Koenig et al.,2000).
- Discovered the connection between angiogenesis and leukocyte adhesion (Melder et al., 1996, Detmar et al., 1998, Moulton et al., 1999).
- Discovered that VEGF upregulates while bFGF downregulates adhesion molecules in vascular endothelium in vitro and in vivo (Melder et al., 1996, Detmar et al., 1998, Jain et al., 1998) and PKCγ, PLD and PKC signaling is involved in inhibition by bFGF (Koenig et al., 2000).
- Developed a physiologically based model of cell biodistribution in mice and humans (Zhu et al., 1996).
- Developed a new method for labeling cells for in vivo biodistribution studies using PET and MRI (Melder et al., 1993, Melder et al., 1994, Schoeph et al., 1998).
- Using a chorioallantoic membrane model and in vivo microscopy, characterized the early events in metastasis and examined the induction of metastasis-related genes (Shioda et al., 1997).
- Showed increased rate of lymphocyte turnover in SIV-injected macaques (Rosenzweig et al., 1998), and differential proliferation in lymphocytes in acute SIV infection (Kaur et al., 2000).
- Demonstrated tumor targeting by salmonella and showed that salmonella accumulation in tumors is due to selective growth in necrotic regions rather than active migration (Forbes et al., 2003).
- Demonstrated that bone marrow stem cells can be labeled with quantum dots for improved in vivo detection (Stroh et al., 2005).
- Quantified bone-marrow cell-derived neovascularization in transplanted and spontaneous tumors and demonstrated its dependence on mouse strain and tumor site (Duda et al., 2005)
- Demonstration that telopeptide-free collagen I enhances RhoA activity and the invasion of a metastatic breast tumor cell line (Demou et al., 2005).
- Demonstrated that platelets play a role in angiogenesis (Kisucka et al., 2006).
- Evaluated circulating endothelial cells (CECs) as a biomarker for antiangiogenic therapy in cancer patients, and characterized the phenotype of CECs (Willett et al., 2004; Willett et al., 2005; Duda et al., 2006).
- Discovered that mechanical compressive stresses can make cancer cells more invasive (Tse et al, 2011).
- Identified the components of tumors that contribute to compressive mechanical stresses in tumors (Stylianopoulos et al., 2012)
- Desmonstrated that targeting cancer-associated fibroblast activity can reduce compressive mechanical stresses in tumors to decompress vessels, increase perfusion, and enhance chemotherapy efficacy (Chauhan et al., 2013)



RESEARCH HIGHLIGHTS

Project 6 Mathematical Modeling

- Developed macro- and microscopic distributed models for antibody distribution in tumors to demonstrate the role of binding (Baxter and Jain, 1991a, Baxter and Jain, 1991b).
- Developed lumped and distributed models for bifunctional antibodies and haptens, and described the data available in the literature (Yuan et al., 1991; Baxter et al., 1992).
- Developed a physiologically-based pharmacokinetic model for antibody using one- and two-step approaches. The model described the data in mice (Baxter et al., 1994) and predicted the human data (Baxter et al., 1995), and allowed dose estimations (Zhu et al., 1997, Zhu et al., 1998).
- Developed a physiologically based model of cell biodistribution in mice and humans (Zhu et al., 1996; Melder et al., 2002; Friedrich et al., 2002).
- Response to anti-VEGF treatment in rectal cancer. Top: before treatment; bottom: after treatment. Arrow shows location of shrinking, more pale tumor.
- Developed a distributed parameter model for microscopic distribution of drugs in ADEPT approach (Baxter and Jain, 1996).
- Developed a poro-elastic model of tumors and suggested a novel strategy to improve the drug delivery to solid tumors (Netti et al., 1995, 1997, 1999).
- Developed the theoretical framework to calculate residual stress in tumors (Skalak et al., 1996).
- Calculated solid stress generated by tumor spheroids (Helmlinger et al., 1997b) and proposed the hypothesis that the tumors lack functional lymphatics due to their collapse by solid stress.
- Developed a novel scheme to quantify the vascular architecture in a tumor (Gazit et al., 1995, 1997). This analysis has allowed us to calculate the role of vascular heterogeneity in nutrient and drug delivery to tumors (Baish et al., 1997, Baish and Jain, 1998, 2000).
- Developed a poro-elastic model for interstitial lymphatic transport (Swartz et al., 1999a).
- Developed a mathematical model for necrosis and dormancy in primary tumors and suppression of angiogenesis in distal tumors based on the transport and generation of angiogenic and anti-angiogenic molecules (Ramanujan et al., 2000).
- Developed a lattice Boltzmann model if leukocyte-RBC-endothelial interaction (Migliorini et al., 2002)
- Developed a linear poroelasticity model for the solid stress generated by spheroid growth as a model of tumor expansion (Roose et al., 2003).
- Developed a mathematical model of the contribution of endothelial progenitor cells to angiogenesis in tumors (Stoll et al., 2003).
- Developed a model for temporal heterogeneities of tumor blood flow (Mollica et al., 2003).
- Used microfluidics to separate blood components (Shevkoplyas et al., 2005).
- Analyzed blood rheology based on the particulate nature of blood using lattice Boltzmann analysis (Sun et al. Biophys. J., 2005).
- Analyzed the effect of erythrocytes in the margination of leukocytes in vessel expansions (Sun et al., Physica A, 2005).
- Provided the first measurements of interstitial hypertension in various human tumors (Boucher et al., 1991, Roh et al., 1991, Gutmann et al., 1992, Less et al., 1992, Jain, 1994c, Boucher et al., 1997, Padera et al., 2002, Willett et al., 2004).
- Analyzed the effects of fiber geometry and charge on drug transport (Stylianopoulos et al Biophys J 2010a, 2010b).
- Developed a 2 parameter model to describe network efficiency (Baish et al., PNAS 2011).
- Predicted that combining 'vascular normalization' and 'stress normalization' can greatly enhance chemotherapy delivery in tumors (Stylianopoulos et al., 2013)

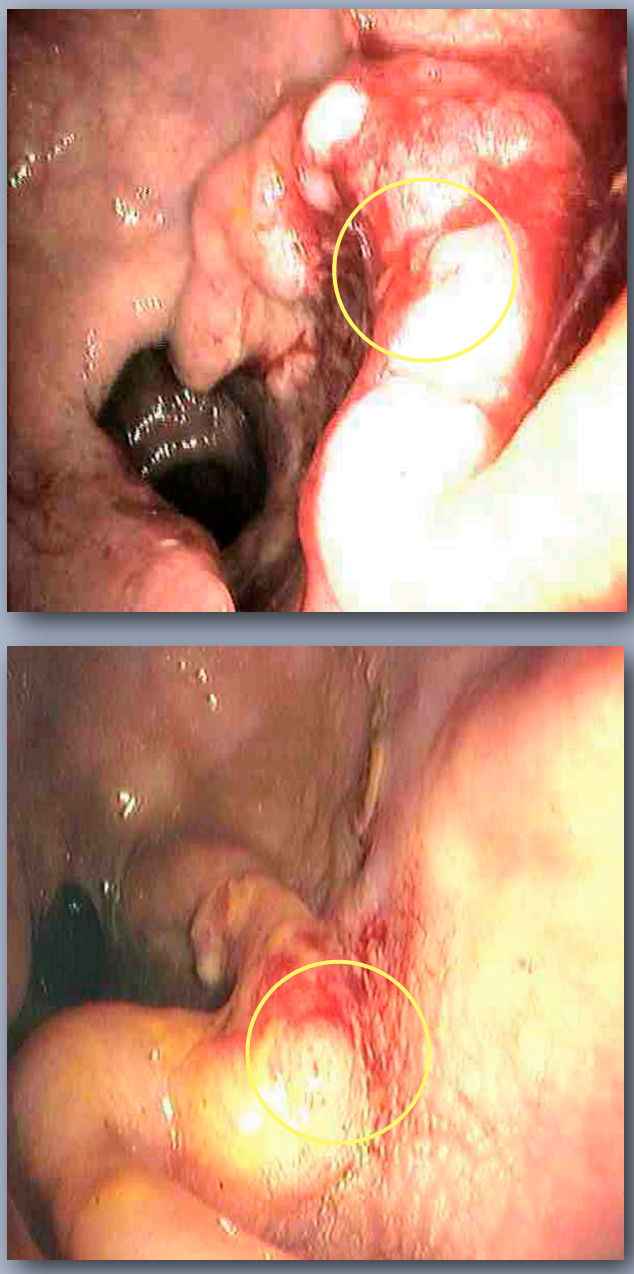


Mathematical modeling of blood flow. Erythrocytes flow from left to right (time sequence--A-D). E-H give the corresponding pressure profiles in the plasma.

RESEARCH HIGHLIGHTS

Project 7 Bench-to-bedside translation

- Provided the first quantitative measurements of geometric resistance to blood flow and of branching patterns in the rat and human tumor vasculature (Less et al., 1997).
- Provided the first glimpse of how anti-angiogenic drug Avastin works in cancer patients (Willett et al., 2004, 2005, 2007).
- Provided the first evidence for vascular normalization by an antiangiogenic agent in rectal carcinoma patients (Willett et al., 2004).
- Demonstrated that VEGF signaling blockade reduces the tumor interstitial fluid pressure in human rectal cancer (Willett et al., 2004; 2005).
- Provided the first evidence that Avastin increases the level of VEGF and PlGF in patients' circulation (Willett et al., 2005).
- Found the presence of PDGFR-β on the lymphatic vessels of Gorham's lymphangiomatosis (Hagendoorn et al., 2006)
- Provided the first evidence that an oral antiangiogenic agent creates a window of normalization in recurrent gliomas and alleviates edema in the brain of these patients (Batchelor et al., 2007). This has led to the recently completed pivotal trial of cediranib in glioblastoma patients.
- Discovered that glioblastoma re-growth after antiangiogenic treatment is associated with increases in plasma levels of bFGF, stromal-derived factor 1 alpha (SDF1α), and blood circulating endothelial cells (CECs) (Batchelor et al., 2007).
- Discovered that liver cancer response may be predicted by MRI and plasma measurements of interleukin 6, and that re-growth after antiangiogenic treatment is associated with increases in plasma levels of interleukin 6, stromal-derived factor 1 alpha (SDF1α), and blood circulating progenitor cells (CPCs) (Zhu et al., 2009).
- Discovered that antiangiogenic therapy with bevacizumab benefits patients with benign tumors (schwannomas)(Plotkin et al., 2009)
- Established a "vascular normalization index" in glioblastoma patients that might predict response to anti-VEGF therapy as early as 1 day after treatment (Sorensen et al., 2009).
- Discovered that blocking VEGF increases SDF1α, CXCR4, NRP-1 and CXCL6 in rectal cancer by laser-capture microdissection in serial patient biopsies (Xu et al., 2009).
- Demonstrated that the brain tumor patients whose tumor blood perfusion improved due to vascular normalization by anti-angiogenic therapy survive longer (Sorensen et al, 2011; Emblem et al, 2013; Batchelor et al, 2013).
- Demonstrated that vascular normalization and not pruning after antiangiogenic therapy with chemotherapy is the mechanism of benefit in breast and lung cancer patients (Heist et al., 2015; Tolaney et al., 2015



Response to anti-VEGF treatment in rectal cancer. Top: before treatment; bottom: after treatment. Arrow shows location of shrinking, more pale tumor.

We are pleased with our progress, which is a result of the hard work, dedication, innovation, organization, and cooperation of the members of the Steele Laboratories, as well as the collaborative support of various members of the MGH/Harvard/MIT community.

Faculty Research Summaries

Tumor Vessels and Microenvironment: Bench to Bedside & Back

Rakesh K. Jain, PhD,A.W. Cook Professor of Tumor Biology

A solid tumor is an organ composed of cancer cells and host stromal cells, which are nourished by the vas–culature and embedded in an extracellular ma–trix. The interaction among these cells, the surrounding matrix, and the local cellular micro–environment influences the expression of certain genes, whose products control the patho–physiological charac–teristics of the tumor, govern tumor prog–ression, and affect the tumor's response to various therapies. Blood and lymphatic vessels also serve as conduits for metastatic spread. The over arching goal of our research is to dissect the pathophysiology of the vascular and extra-vascular components of tumors, to determine the role of tumor-host interactions in tumor biology, and ultimately to translate this knowledge into improved cancer detection, prevention, and treatment in humans.

To unravel the complex biology of tumors, we have developed an array of imaging technologies, mathematical models, and sophisticated animal preparations. These include multiphoton microscopy and genetically engineered mice with surgically implanted transparent windows, which permit the in vivo visualization of gene expression and function in tumors and their surrounding host stroma. This undertaking has provided unprecedented molecular, cellular, anatomical, and functional insights into the vascular, interstitial and cellular barriers to cancer treatment.

Our laboratory found that high interstitial pressure is a universal characteristic of solid tumors, and that it can impair the delivery of molecular medicine within tumors, induce peri-tumor edema and contribute to lymphatic metastasis. We have identified the mechanisms underlying this elevated pressure: high vascular permeability, lack of functional lymphatics, and mechanical stress generated by tumor growth. Overexpression of the lymphangiogenic factor VEGF-C increases lymph node metastasis, but does not increase lymphatic function or decrease the interstitial pressure. However, judicious application of antiangiogenic agents can lower the pressure and improve the delivery and efficacy of various cancer treatments. To gain a deeper insight of tumor microenvironment, we measured interstitial convection, diffusion, and binding using photobleaching, and pO2 and pH profiles around individual tumor vessels using phosphorescence quenching and ratio imaging. We proposed the novel hypothesis that the anomalous assembly of the collagen network can prevent the penetration of therapeutic agents in tumors, and showed that the hormone relaxin, bacterial collagenase, MMP1/8 and anti-hypertensive drugs can improve drug distribution by modifying this network.

Our finding that angiogenic molecules regulate adhesion molecules on the vasculature provided the first link between the disparate fields of angiogenesis and adhesion, and revealed a novel mechanism by which tumors evade immune recognition. In collaboration with Dr. Brian Seed, we discovered that cancer cells co-opt the host stromal cells and entice them to produce pro- and anti-angiogenic growth factors. By revealing that host cells are not passive bystanders, but active participants in tumor angiogenesis, growth, metastasis, and therapeutic response, our laboratory provided a rational basis for combining Herceptin with VEGF blockade for the treatment of breast cancer - a concept that led to a clinical trial.

Our work has revealed that the malfunction of the vascular and extravascular compartments in solid tumors often thwarts the effectiveness of both conventional and novel therapies. Our laboratory is most celebrated for a new hypothesis that antiangiogenic therapy can "normalize" the abnormal tumor vasculature and matrix, and thus improve both the delivery and efficacy of therapeutics. We have validated these concepts in multiple clinical trials and identified candidate biomarkers for improving treatment.

By integrating principles from physiology, pharmacology, immunology, and molecular biology, our laboratory has developed mathematical models of drug delivery and pathophysiological processes in solid tumors. These modeling tools have allowed us to extract simple, important principles that should spark the development of novel diagnostic and therapeutic strategies.

Selected Publications

- Incio J, et al. Obesity-induced inflammation and desmoplasia promote pancreatic cancer progression and resistance to chemotherapy. Cancer Discovery 6: 852–869 (2016).
- Jain RK. Antiangiogenesis strategies revisited: From starving tumors to alleviating hypoxia. Cancer Cell 26: 605–622 (2014).
- Jain RK. Normalizing tumor microenvironment to treat cancer: Bench to bedside to biomarkers. J Clinical Oncology 2013; 31:2205-18.
- Snuderl M et al. Targeting placental growth factor/neuropilin 1 pathway inhibits growth and spread of medulloblastoma. Cell 2013; 152: 1065–1076.
- Batchelor TT, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007; 11: 83-95.
- Jain RK. Normalization of the tumor vasculature: An emerging concept in anti-angiogenic therapy. Science 2005; 307:58-62
- Willett C, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nature Medicine 2004; 10:145-147.
- Koike N et al. Engineering long-lasting blood vessels. Nature 2004; 428:138-139.
- Padera TP, et al. Lymphatic metastasis in the absence of functional intratumor lymphatics. Science 2002; 296:1883 1886.
- Izumi Y, et al. Herceptin acts as an anti-angiogenic cocktail. Nature 2002; 416: 279-280.
- Fukumura D, et al. Tumor induction of VEGF promoter activity in stromal cells. Cell 1998; 94:715-725.]

The Modulation of Tumor Desmoplasia Improves Vascular Perfusion, and the Delivery and Effectiveness of Therapeutics in Tumors.

Yves Boucher, PhD; Associate Prof., Radiation Oncology

The elevated fibrillar collagen content – associated with tumor desmoplasia – is a significant barrier to drug delivery in several tumor types. We recently found that the anti-hypertensive agent losartan produces a dose-dependent reduction in stromal collagen in several tumor models – including pancreatic ductal adenocarcinoma (PDAC) in mice. Furthermore, losartan improved vascular perfusion, the distribution and therapeutic efficacy of oncolytic viruses, Doxil and small cytotoxic agents in PDAC and breast cancer models. Furthermore, based on our experimental results with losartan, we initiated a clinical trial at Massachusetts General Hospital to determine in patients with PDAC whether losartan improves the efficacy of the drug cocktail FOLFIRINOX.

The Targeting of Cancer Cells and Tumor Blood Vessels Improves the Spread and Efficacy of Oncolytic Virus. Phase I/II trials have shown that the intravenous injection (i.v.) of oncolytic viruses is safe and leads to virus delivery / infections in tumor lesions. Nevertheless, the i.v. delivery of therapeutic doses of oncolytic viruses remains a challenging task. The relatively large size of viral particles hinders their passage through the wall of tumor vessels, the extracellular matrix and in narrow spaces between cancer cells. We previously showed that the induction of tumor cell apoptosis enhances the spread and effectiveness of oncolytic viruses injected intratumorally. We recently tested the hypothesis that the HSP90 inhibitor Ganetespib – a potent inducer of apoptosis – would induce endothelial apoptosis, thus increasing the permeability of tumor vessels and the intratumoral distribution and efficacy of oncolytic viruses (Han, in preparation). In vitro, Ganetespib increased the permeability of endothelial monolayers. However, Ganetespib did not induce endothelial cell apoptosis, but increased the phosphorylation of VE-cadherin, which was associated with the disruption of endothelial adherent junctions. In breast cancer models Ganetespib enhanced the phosphorylation of VE-cadherin – suggesting a disorganization of endothelial adherens junctions in tumor vessels – and increased the intratumoral penetration of nanoparticles and spread of oncolytic virus. Ganetespib combined with a relatively low dose of oncolytic virus injected i.v. induced tumor regressions, increased overall survival and produced cures in breast cancer models.

Fibroblast and Cancer Cell Migration and Extracellular Matrix Remodeling. I developed with collaborators a new optical imaging approach to track – for the first time – the slow in vivo movement of tumor-associated fibroblasts (TAFs) and collagen fiber remodeling by TAFs. Using this approach we showed in tumors that integrin b1 is required for the close interaction between collagen fibers and TAFs, while matrix metalloproteinases (MMPs) and integrins play a role in TAF-remodeling of collagen. While MMPs affect cancer cells and TAF migration, the relative stiffness of the tumor matrix can also influence cancer cell migration. In another stydy we demonstrated that the stiffness of collagen fibers restricts the RhoA-dependent amoeboid movement of cancer cells. We found recently that TAFs isolated from human breast cancer samples enhance RhoA/ROCK signaling and amoeboid movement. The crosstalk between CAFs and breast cancer cells increased the secretion of insulin growth factor (IGF-1) in CAFs and plasminogen activator inhibitor-1 (PAI-1) activity in cancer cells. Interestingly, both IGF1 and PAI-1 activated RhoA signaling in cancer cells, which promoted cell scattering and amoeboid invasion. In another project we explored the role of membrane-type 1 matrix metalloproteinase (MT1-MMP) in vascular invasion and metastasis. The down-regulation of MT1-MMP in cancer cells decreased the spontaneous formation of lung metastases from mammary tumors without affecting lymph-node metastasis. This occurs because MT1-MMP down-regulation decreased blood, but not lymphatic, vessel intravasation. In breast cancer biopsies, the expression of MT1-MMP in triple-negative breast cancer correlated with blood vessel invasion. Thus, MT1-MMP expression could be tested as a therapeutic target and biomarker of blood-borne metastasis in TNBC.

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Role of Tumor-Stroma Interactions in Cancer Progression and Treatment

Dan G. Duda, DMD, PhD, Associate Prof., Radiation Oncology

The goal of my research is to gain fundamental insight into solid tumor cellular biology. My areas of expertise are 1) the biology of local-derived stroma (tumor-associated vessels, fibroblasts) and distant stroma (bone marrow-derived cells or BMDCs) in tumor progression; and 2) the development of predictive biomarkers for targeted therapies for cancer. I aim to translate this knowledge into improved therapies by conducting preclinical and clinical studies in collaboration with MGH clinicians. I am currently leading the following projects:

1. Overcoming Evasion from Sorafenib Treatment in Hepatocellular Carcinoma (HCC)

Sorafenib is the first systemic therapy approved for HCC. However, HCC rapidly evade sorafenib treatment, despite its multi-targeted activities. We are studying the pathways of evasion from sorafenib in HCC (P01/PPG Project 3). We are examining the role of MEK/ERK activation as a cell autonomous mechanism of escape. We are also studying how sorafenib-induced changes in HCC stroma lead to stromal-derived growth factor 1 alpha (SDF1-alpha/CXCL12)-mediated changes in vascular structure and function, inflammation/bone marrow-derived cell infiltration and fibrosis, and if these mediate HCC escape from treatment. To this end, we have developed orthotopic models of metastatic HCC in immunocompetent mice (Fig. 1), and have developed and acquired spontaneous genetically engineered mouse models of HCC through our collaborations at MGH Cancer Center.

In parallel, we are exploring the potential roles of stroma-derived factors in HCC patients treated with sora-fenib and other anti-angiogenic agents in collaboration with Dr. Zhu of the MGH Cancer Center.

2. Impact of Tumor Stroma Activation after Radiation Therapy on Local Tumor Control and Metastasis

We and others have found that SDF1-alpha/CXCR4 and HGF/cMET pathways can be activated by ionizing radiation in tumor stroma. Thus, we are currently evaluating the role of SDF1-alpha/CXCR4 or HGF/cMET inhibition as a sensitizer for radiation therapy in preclinical models. Specifically, we are examining 1) the role of SDF1-alpha and its receptors CXCR4 and CXCR7 in progression to metastasis after local radiotherapy (supported by an R01 grant); 2) the role of CXCR4 and bone marrow-derived cells in bone metastatic escape from palliative radiotherapy (funded through an ACS grant); and 3) the role of cMET inhibition in combination with radiotherapy in metastatic pancreatic adenocarcinoma models (supported by a Cummings Foundation grant). To this end, we have developed orthotopic models of prostate cancer, including a calvarial tumor model, which allows intravital microscopy imaging as well as orthotopic models of pancreatic adenocarcinoma.

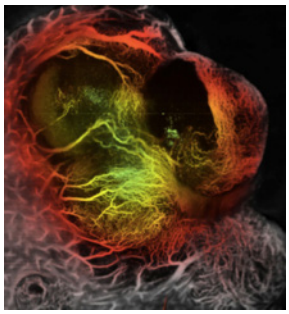

Fig. 1: Representative in vivo microscopy image of hepatocellular carcinoma growing in the liver of a mouse; in red, functional tumor blood vessels imaged by optical frequency domain imaging.

In parallel, we are exploring the potential roles of SDF1-alpha/CXCR4 and HGF/cMET in prostate carcinoma, pancreatic adenocarcinoma, and HCC patients treated with radiotherapy in collaboration with MGH Cancer Center clinicians Drs. Efstathiou, Zhu and Hong (funded through NCI/Proton Beam Federal Share Program grants).

3. Biomarkers of Treatment Response

This project is carried out in the context of a large effort of clinical correlative studies (in over 35 clinical trials of antiangiogenic agents and/or radiotherapy), which include imaging, tissue and blood biomarker studies. This involves large teams of clinicians at MGH and Dana Farber Cancer Institute, and is funded through multiple collaborative grants from the NCI, DoD and NFCR. We are primarily focusing on the potential predictive biomarker value of circulating immune cells as well as proteins – soluble vascular endothelial growth factor (VEGF) receptor 1 (sVEGFR1 or sFLT1), as well as on the potential role of SDF1-alpha and HGF – as biomarkers of escape from anti-VEGF therapies or radiotherapies.

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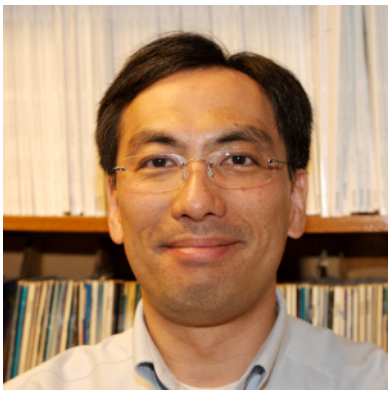
Angiogenesis and Microcirculation in Physiological and Pathophysiological Settings



Dai Fukumura, MD, PhD;Associate Professor of Radiation Oncology

The long-term goal of my research is to uncover the fundamental nature of vascular biology in both physiological and patho-physiological settings, and to utilize this knowledge for detection and treatment of diseases. Together with outstanding collaborators, I have been developing and utilizing state of the art imaging techniques and animal models which led to the discoveries summarize below.

Role of NO in tumor angiogenesis, lymphangiogenesis, microcirculation and radiation therapy

Nitric oxide (NO) is a highly reactive mediator with a variety of physiological and pathological functions. NO increases and/or maintains tumor blood flow, decreases leukocyte-endothelial interactions, and increases vascular permeability and thus, may facilitate tumor growth. Furthermore, NO mediates angiogenesis and vessel maturation predominantly through endothelial NO synthase. We also found that NO mediates lymph-angiogenesis and metastasis as well as function of lymphatic vessels. We recently uncovered that restoration of perivascular NO gradients improves structure and function of both blood and lymphatic vessels, and response to radiation.

Role of tumor-host interactions in angiogenesis, tumor growth and metastasis

Using genetically engineered mouse and tumor models as well as in vivo imaging techniques, we found for the first time that nontransformed stromal cells –including activated fibroblasts, bone marrow derived cells – are a major inducer of tumor angiogenesis and mediate the formation of abnormal microenvironment. Furthermore, various anti-angiogenic or molecularly targeting treatments result in the activation of host stromal cells leading to treatment resistance. Our recent data indicate that stromal cells in the primary tumor travel with tumor cells and facilitate survival and growth of metastatic tumors. Controlling tumor-host interaction is an promising approach to facilitate tumor treatment. For example,, the blockade of vascular endothelial growth factor signaling can transiently normalize tumor vasculature and potentiate anti-tumor cytotoxic therapies.

Probing tumor microenvironment using nanotechnology

We have been studying the tumor microenvironment and transport properties using nano-probes. We found that relatively large nanoparticles – size of current nanomedicine – can take advantage of enhanced permeability and retention effect for transvascular transport but are unable to penetrate into tumor tissues. We also found superior transvascular transport of rod-shape over spherical nanoparticles. Furthermore, we discovered that neutral charge is the best for interstitial transport. These findings led us to develop multistage nanotherapeutics that shrink upon the entry to the tumor microenvironment in order to facilitate interstitial transport.

Role of obesity in angiogenesis, tumor growth and treatments.

First, we established in vivo system to investigate blood vessel formation during adipogenesis. Using genetic inhibition of PPARγ and pharmacological inhibition of VEGFR2 signaling we found provocative reciprocal regulation of adipogenesis and angiogenesis, suggesting a novel strategy to treat obesity related diseases including cancer. We then established a physiologically based mathematical model and found that leptin pathway plays a key role in maintenance of body mass and its disruption destroys the body weight balance. We are currently studying the underling mechanisms of obesity-induced aggravation of breast cancer through both preclinical studies and clinical trials of breast cancer patients.

Engineering blood vessels

A major limitation of tissue engineering is the lack of functional blood and lymph vessels. First, we established a model to monitor tissue engineered blood vessels in vivo using MPLSM. We found that mesenchymal precursor cells accelerate remodeling of 3-D endothelial cell structure to functional blood vessels, differentiate into peri-vascular cells, and stabilize engineered vessel network for up to a year. Using this tissue engineered blood vessel model,.we then, showed that human ES cell, cord blood and peripheral blood -derived endothelial cells form functional blood vessels in vivo and that human bone marrow derived mesenchymal stem cells serve as perivascular precursor cells, mature and stabilize blood vessels. Detail observation of vessel anastomosis in these tissue-engineered blood vessels revealed a novel mechanism – wrapping-and-tapping of host vessels. More recently, we have established robust protocols deriving endothelial cells and mesenchymal precursor cells from induced pluripotent stem (iPS) cells and successfully generated blood vessels these iPS-derived cells.

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Cancer Metastasis

Igor Garkavtsev, MD, PhDAssistant Professor, Radiation Oncology

Our research focuses on mechanisms governing the development of brain tumors, with primary emphasis on the identification and character-ization of novel tumor sup-pressor genes. We are particularly interested in understanding how these genes are involved in the regulation of brain tumor angiogenesis and invasion. A detailed understanding of this regulation may lead to the rational selection of molecular targets for anti-cancer drug development.

Gliomas are the most common primary tumors of the central nervous system, with nearly 15,000 diagnosed annually in the U.S. and a mortality approaching 80% within the first year after diagnosis. Malignant gliomas are very aggressive, highly invasive, and one of the deadliest of human cancers. Glioblastomas have been linked to the inactivation of the

Cancer Stem Cells

Tumors contain tumorigenic cancer cells, termed "tumor-initiating cells" (TICs), which are capable of both replenishing themselves and giving rise to populations of nontumorigenic cancer cells (non-TICs). The molecular mechanisms responsible for tumor initiation remain poorly understood. We found molecular mechanism that esponsable for tumor initiation. We performed chemical screening strategy to identify small molecules that enhance the effect of chemotherapeutic agents on TIC-enriched breast cancer cells. We identified proteins that interact with the lead compound C108, including the stress granule-associated protein, GTPase-activating protein (SH3 domain)-binding protein 2, G3BP2. G3BP2 regulates breast tumor initiation through the stabilization of Squamous cell carcinoma antigen recognized by T cells 3 (SART3) mRNA, which leads to increased expression of the pluripotency transcription factors Octamer-binding protein 4 (Oct-4) and Nanog Homeobox (Nanog). Our findings suggest that G3BP2 is important for the process of breast cancer initiation. Furthermore, these data suggest a possible connection between stress granule formation and tumor initiation in breast cancer cells.

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Spontaneous Tumors and their Isograft Models: Histopathology/Pathophysiology Studies and Applications in Experimental Cancer Therapy

Peigen Huang, MD, PhDAssistant Professor, Radiation Oncology

First, our research focuses on the development of spontaneous tumors in mice and on how the age, genetic background, and immune status of the mice - as well as the presence or absence of specific genes affect the histopathological characteristics of the tumors.

We study the incidence of spontaneous tumors and their pathological pattern in the natural setting of aged mice, which are kept alive for nearly their full normal life span. The animals are raised within a gnotobiotic colony that is free of life shortening intercurrent infectious diseases. We have found a high incidence of subcutaneous sarcoma in our aging C3Hf/Sed female mice.

In our aging, retired FVB/N breeder mice, tumors are most commonly found in the lungs. The incidence of spontaneous T-cell thymic lymphomas in severe combined immunodeficient (SCID) mice is strikingly high. We have also published the first comprehensive report of spontaneous nonthymic tumors, including 8 myoepitheliomas and 3 rhabdmoyosarcomas, from our SCID retired breeders. Our results show that the incidence of spontaneous tumors and their morphological changes are markedly strain dependent, and are immune status as well as age associated. We are also documenting the development, growth, and histopathological characteristics of spontaneous tumors in the GFP transgenic mice with FVB background (such as VEGF-GFP/FVB, and Tie2-GFP/FVB mice). Our goal is to test the hypotheses that (a) the insertion of GFP reporter genes affects the incidence of spontaneous tumors in aging FVB genotobiotic mice, as well as changes their pathological patterns, and (b) spontaneous tumors developed in FVB-GFP transgenic mice exhibit different biological and molecular biological characteristics, such as different growth and metastatic potential, and different GFP expression in tumors as compared to the tumors in wild-type FVB mice.

Second, we are interested in developing novel tumor lines that are derived from the spontaneous tumors found in our laboratory. These tumor lines are used to study tumor pathophysiology in specific strains of transgenic mice derived from the same genetic background as the spontaneous tumors. One of our tumor lines, Os-P0107, is derived from a spontaneous osteosarcoma in a VEGF-GFP transgenic mouse; each of the cells in an Os-P0107 tumor expresses green fluorescent protein (GFP), which makes them easy to locate and track with intravital microscopy. Another tumor line, LAP0297, is a lung adenocarcinoma with a high incidence of distant lung metastases. This line, which is ideal for the study of metastasis, is derived from a spontaneous lung tumor in a FVB/N mouse. For pre-clinical studies of antiangiogenesis therapy, we have used spontaneous autochthonous tumors and their isografts, implanted in aged C3Hf/Sed mice, to more accurately simulate the clinical conditions that affect many human cancer patients.

Most recently, we established and characterized two novel in vitro and in vivo tumor models (MCa-M3C and MCa-PSTC) from the spontaneous adenocarcinomas arising in MMTV-PyVT/FVB transgenic mice. MCa-M3C is a high-selected neu-positive metastatic mammary tumor line, which has been considered a very useful model for several new research projects in our laboratory. We have made significant progress in the studies of combining Losartan with radiotherapy for the treatment of MCa-M3C metastatic breast cancer, resulting significantly decreased MCa-M3C MFP-to-lung macro metastases and increased host survival.

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Complete List of Published Work in My Bibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/1hi7il5Ffx3kG/bibliography/46868120/public/?sort=date&direction=ascending

Blood dynamics and Tumor Physiology

Lance L. Munn, PhD
Associate Prof., Radiation Oncology

My research focuses on blood vessel structure and function in normal and pathological conditions. Within this broad area, I have projects that address:

Angiogenic sprouting
During angiogenesis, endo-thelial cells abandon their normal arrangement in the vessel wall to migrate into the extravascular matrix. This process is controlled by multiple signals and is necessary for tissue regeneration and tumor growth. Using in vitro models and microfluidic devices, we are investigating the biochemical and mechanical determinants of this morphogenic transformation.

Vascular anastomosis

In order to form new, patent blood vessels, angiogenic sprouts must connect. The process by which this happens --anastomosis -- is poorly understood, but represents new targets for vascular therapy. Using intravital microscopy and engineered vascular devices, we are following the steps of anastomosis to identify cellular and molecular mechanisms that may eventually be targeted for enhancing wound healing or inhibiting pathological angiogenesis.

Blood vessel remodeling

In many normal physiological responses, endothelial cells and the blood vessel networks they form undergo dramatic changes in morphology and function. Examples include angiogenesis in wound healing, vessel dilation/hyperpermeability in inflammation, and endometrial angiogenesis in the female reproductive cycle. Endothelial cells, in cooperation with other stromal cells, have to accomplish these diverse changes by responding to a limited number of growth factors including VEGF, PlGF and bFGF. We are using a systems biology approach to understand how the various growth factors and cells cooperate to produce these seemingly diverse functions. Because tumor angiogenesis relies on many of these same growth factors and cellular mechanisms (but in an abnormal, poorly controlled way), these studies will allow a better understanding of tumor angiogenesis and anti-angiogenic therapy.

Cancer cell invasion

During the initial stage of metastasis, cancer cells must breach the vessel wall and enter the circulation. Despite intense research in this area, the cellular mechanisms by which this occurs are poorly understood. Some tumors seem to metastasize as single rogue cells, while others travel in groups or clusters; some seem to actively migrate into the vessel, while others may be passively pushed. Using gene array analysis and carefully designed coculture systems, we are assessing the mechanical and cellular determinants of the initiation of metastasis.

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The lymphatic system in disease processes and cancer progression

Timothy P. Padera, PhD
Associate Prof., Radiation Oncology

Lymphatic vessels are responsible for draining interstitial fluid from tissues and for transporting immune cells to lymph nodes to maintain the body's immune surveillance. Thus, lymphatics are important in maintaining both tissue fluid balance and proper function of the immune system. Predictably, disruptions of the lymphatic system lead to lymphedema and the conditions for chronic infections. Lymphatic vessels also facilitate the dissemination of cancer cells from a primary tumor to regional lymph nodes. My research group looks to

understand the mechanisms behind the growth, maturation and function of lymphatic vessels and how these mechanisms can contribute to the pathogenesis of lymphedema, chronic infections and cancer dissemination.

In order to study the role of the lymphatic system in a variety of disease states, we have developed novel animal models which mimic certain aspects of human disease. Using intravital microscopy, we have investigated the individual steps of lymphatic metastasis. We can monitor the lymphatic vessels in the tumor margin, observe tumor cells moving in lymphatic vessels, measure lymph flow and quantify the number of tumor cells that arrive in the draining lymph node. Our studies have shown that tumors lack functional intratumor lymphatic vessels due to compressive forces inside tumors that cause their collapse. Our studies have also shown that VEGF-C, which is associated with lymphatic metastasis in patients, increases the size of the tumor margin lymphatic vessels, making them more vulnerable to invasion. Our data suggests that VEGF-C needs to be blocked very early in the metastatic process to be able to reduce VEGF-C enhanced lymphatic metastasis. Furthermore, we have shown that VEGFR targeted agents are not effective in preventing the growth of cancer cells that have seeded the lymph node, questioning the ability of these therapies to be used in the adjuvant setting.

To further study the growth of metastasis in the lymph node, we have developed a novel model that allows chronic imaging of a tumor draining lymph node. Using our model, we have shown that lymph node metastases do not require sprouting angiogenesis in order to grow. Thus, we have shown that lymph node metastases do not respond to anti-angiogenic therapies, identifying one possible mechanism of the lack of efficacy of anti-angiogenic therapy in patients.

In addition, we have begun to study the pathogenesis of lymphedema by unraveling the molecular underpinnings of autonomous contraction of collecting lymphatic vessels using a novel animal model. We have shown that the spatial and temporal gradients of nitric oxide, which are disrupted during inflammation, are critical for lymphatics to drive lymph forward. Furthermore, when lymphatic contractions are disrupted, the immune response to a foreign antigen is muted. Thus disruption of lymphatic function has consequences for the overall immune function. We will test whether cancer or bacterial infections invoke similar regulatory dysfunction of lymphatic contraction. This work may lead to new targets to combat lymphedema and infections.

In order to better understand the relationship between lymphatic vessel contraction and lymph flow, we have developed the first method to measure dynamic lymph flow in vivo without the need for injected contrast. Our future studies will continue to dissect the physical and molecular determinants of lymphatic vessel function, lymph flow, lymphangiogenesis and lymphatic metastasis. Through the use of our novel imaging technologies and animal models, we will answer timely questions that can lead to the development of treatments for lymphedema, chronic infections and lymphatic metastasis.

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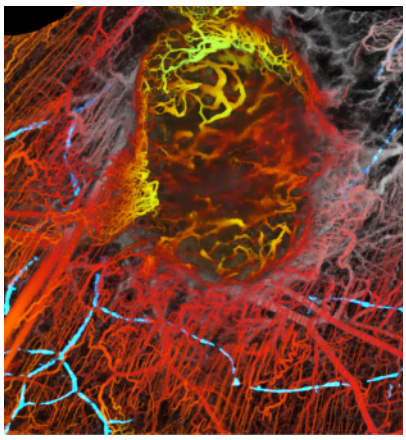
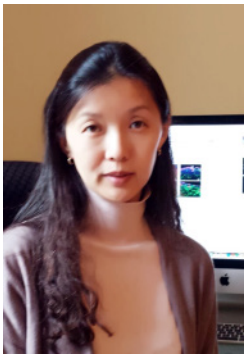


Tumor vasculature and lymphatics imaged using OFDI

Tumor-Host Interaction in Tumor Angiogenesis and Metastasis



Lei Xu, MD, PhD
Assistant Professor, Radiation Oncology

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:

Overcoming chemoresistance in human ovarian cancer

One aspect of my research interest is in the role and the molecular mechanism of miRNA in cancer metastasis and chemoresistance. Chemoresistance remains a major obstacle to successful cancer treatment. Chemoresistance may be due to increased drug efflux, dysregulated DNA repair and decreased tumor cell apoptosis. Our exciting preliminary findings show that microRNA-155 (miR-155) directly targets X-linked Inhibitor of Apoptosis Protein (XIAP) and mdr1/P-glycoprogein (P-gp). XIAP inhibits the apoptotic pathway and P-gp exports drugs and decreases their cellular accumulation, both are important mediators contributing to chemoresistance. We propose to investigate if miR-155 increases chemosensitivity via negative regulation of XIAP and P-gp, which increase chemo-induced apoptosis and decreases drug efflux.

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.

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.

Mechanism of evasion from anti-angiogenic treatment

At the same time, I also study the host contribution to tumor progression. In particular, I studied NK cell, an important component of the innate immune system, recruitment and function affected by anti-angiogenic therapy. We found that anti-angiogenic therapy increased NK cell recruitment and enhanced its cytotoxic activity.

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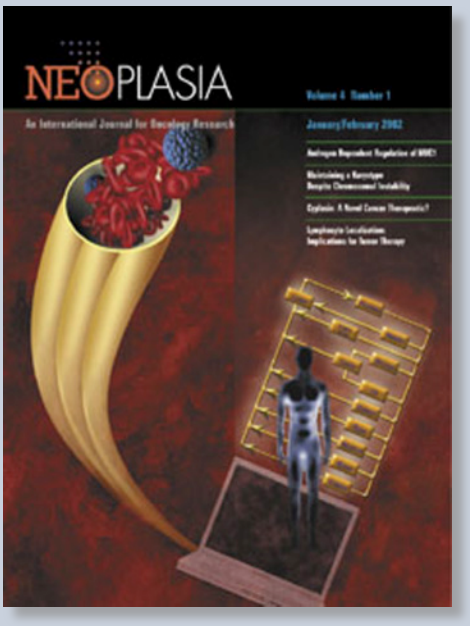

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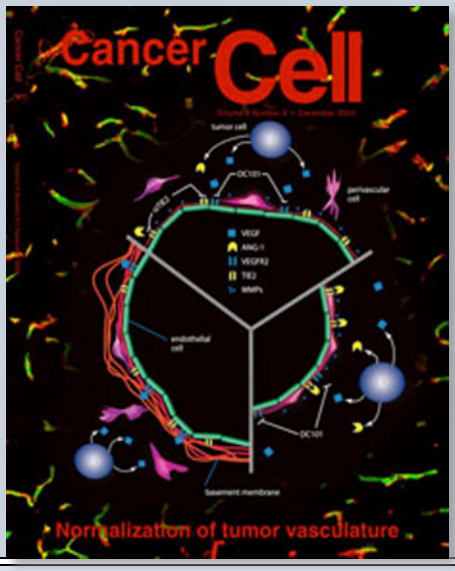

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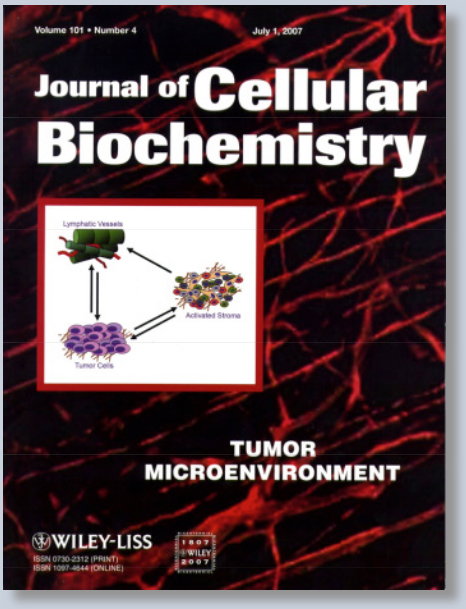

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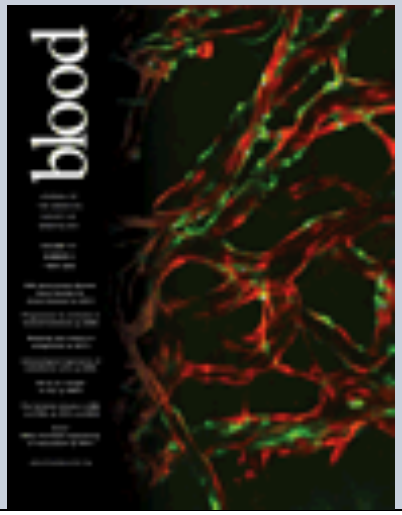

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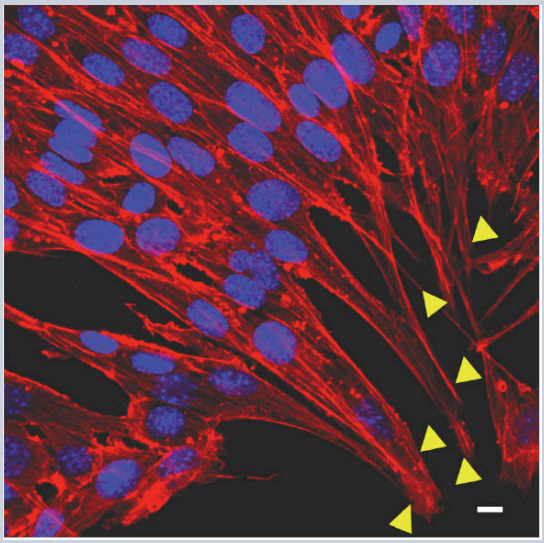

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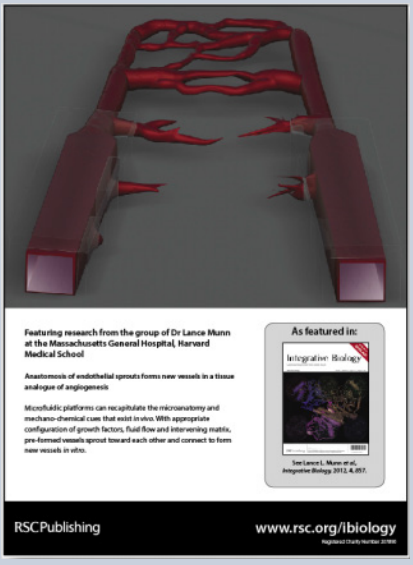

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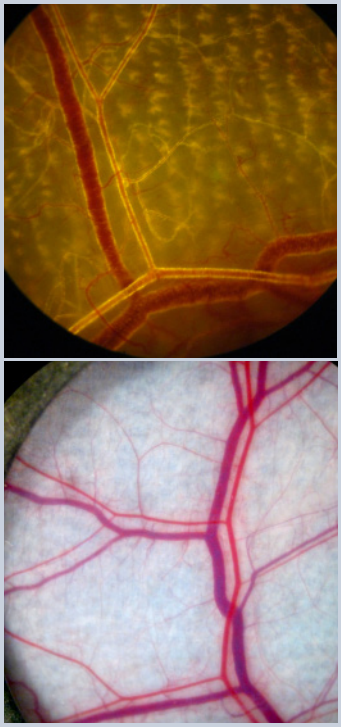

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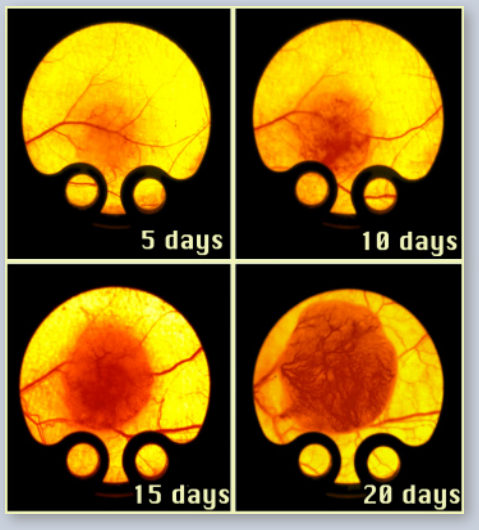

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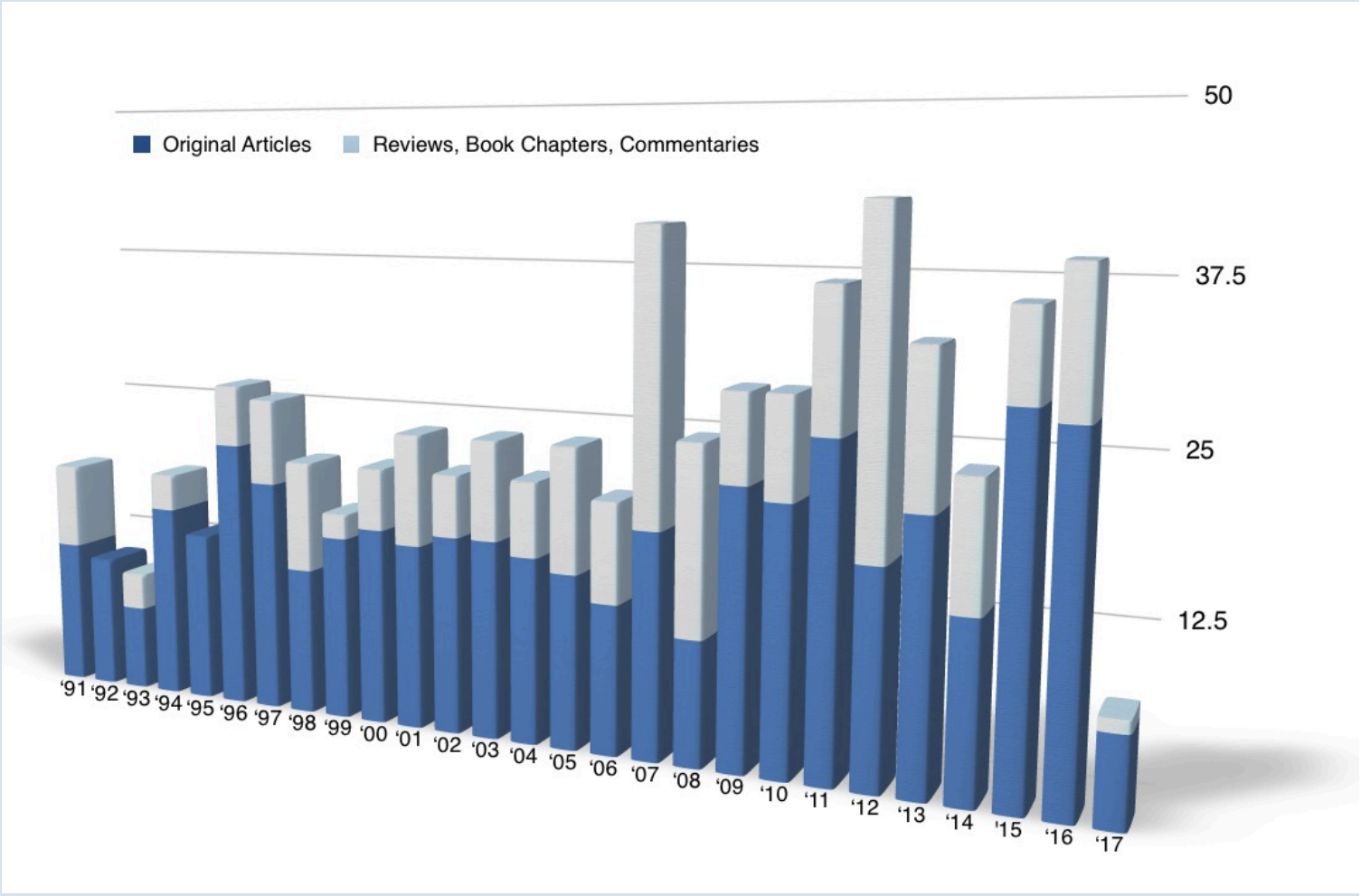

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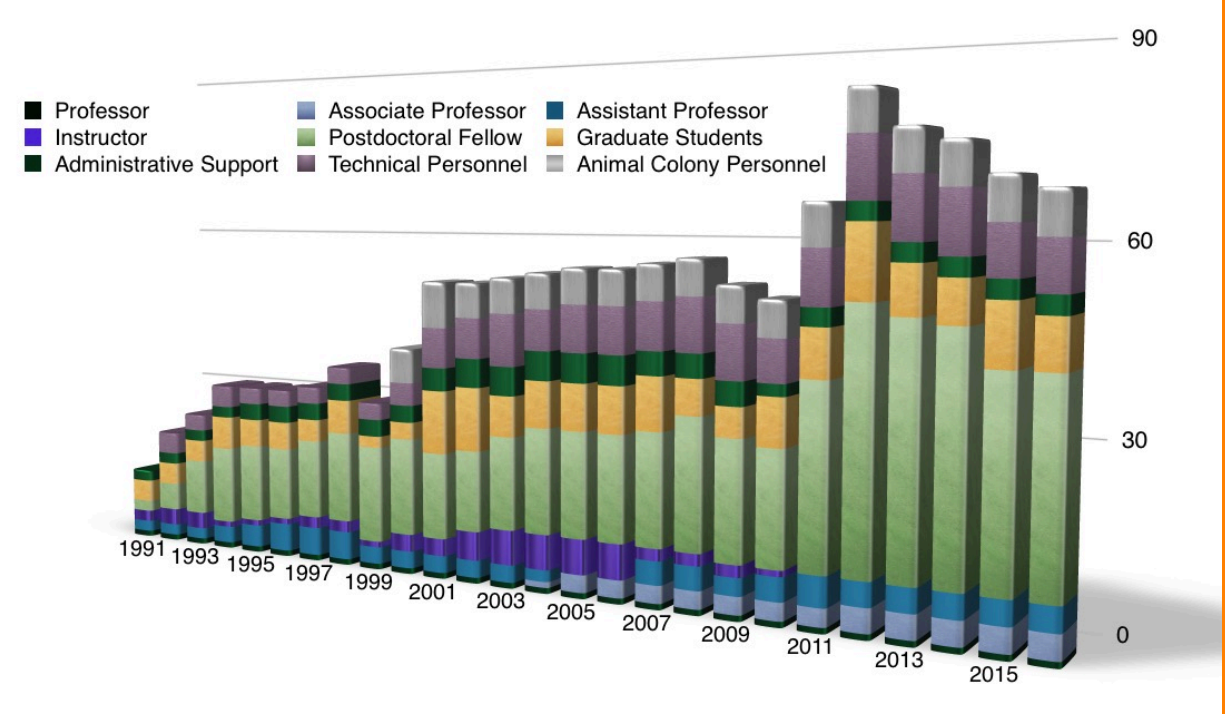
RESEARCH TEAM

In September 1991, we started with a small team of six people, and we have since grown to approximately 90 members, and have developed a leading, multidisciplinary research and education program in the integrative biology of cancer. We have trained more than 200 graduate and post-graduate students - several of them have become leaders in academia, government and industry.



ALUMNI

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Anders Leu	1993 - 94
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Cecilia Capello	1994
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Ricky Tong	2001 - 05
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Ryan Lanning	2003 - 09
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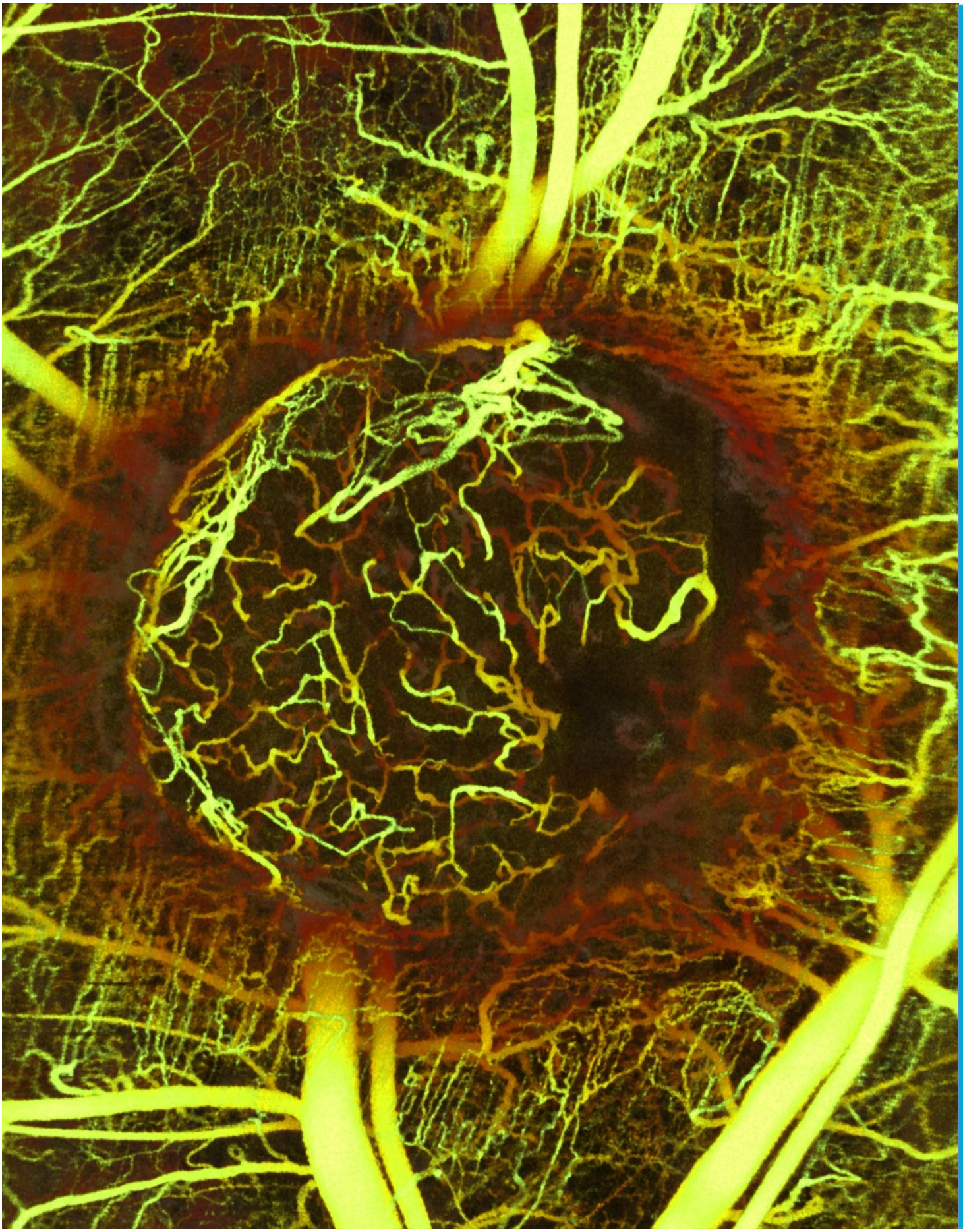
Vikash Chauhan	2006 - 12
Benjamin Diop - Frimpong	2007 - 10
Ming - Zer Poh	2007 - 09
Janet Tse	2007 - 11
Abhishek Jain	2008 - 12
Jieqion (Jane) Liu	2009 - 12

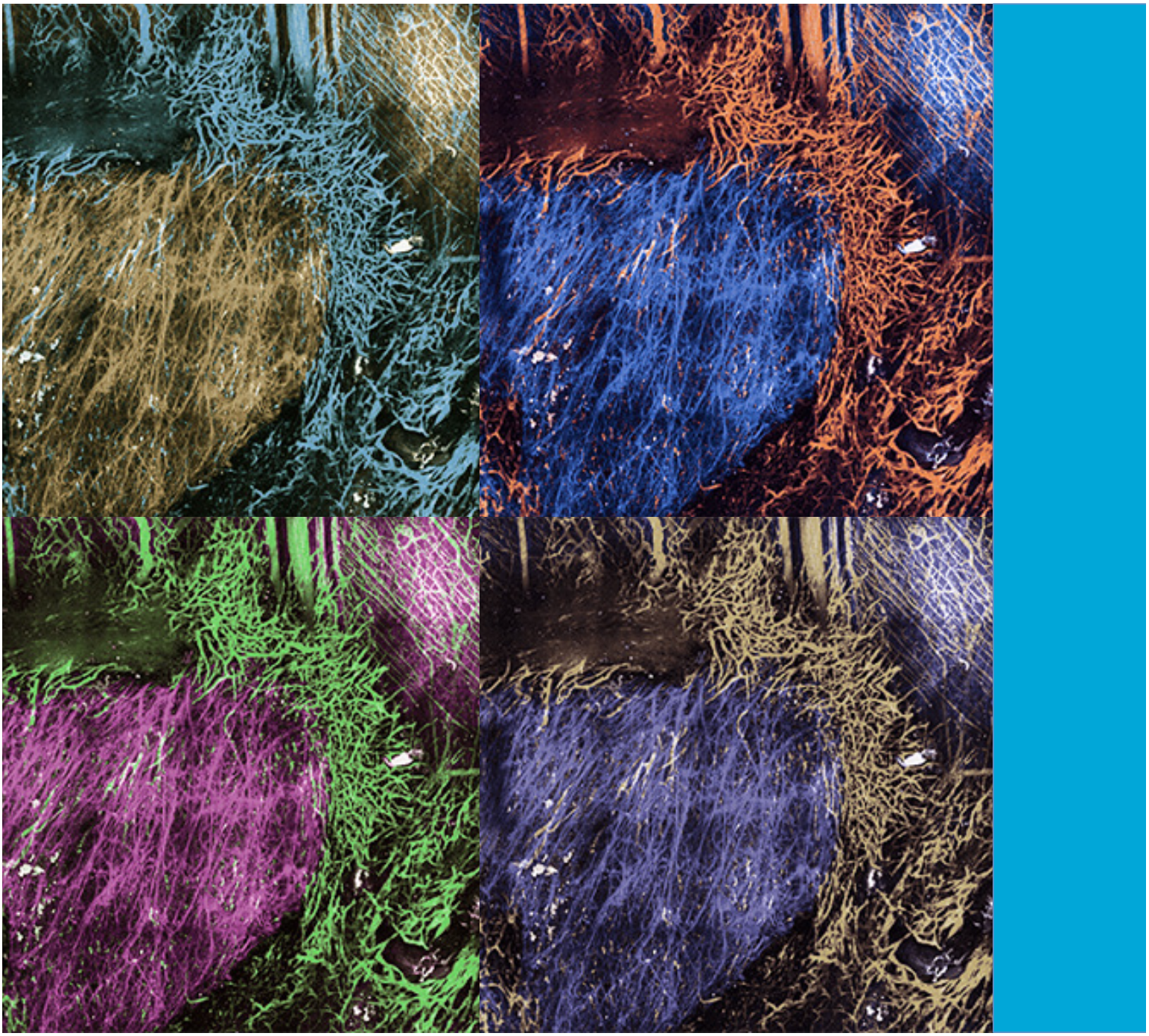
Chun Li	2009
Elisabeth Niemeyer	2010 - 11
Vikash Chauhan	
John Martin	
Kamila Naxerova	
Teresa Peterson	
Koen Marijt	
Research Assistants	
Eric Kaufman	1988 - 92
Patrick Yoon	1993
Peter Khalifah	1993 - 93
G. Ray Martin	1994
Luke Wang	1995
Valerie Verdier	1995 - 96
Visiting Scholars	
James Baish	1994, 2013
Catharina Davies	1997 - 98
John Tarbell	1997 - 98
Donald Buerk	1998 - 99
Robert Feil	2012 - 13

RESOURCES AND ENVIRONMENT

The Steele Laboratories are located at two different sites. A facility for defined flora and immunodeficient rodents and about 1500 ft^2 of laboratory space, including two microscopy suites and multipurpose bench area and offices, are located at the Massachusetts General Hospital (MGH). Additional laboratory space (approximately 5,000 ft^2) which includes a microscopy suite, tissue culture facility, surgical area, clinical research studies, multipurpose bench space and offices, is located at the MGH-East facility in Charlestown. Investigators divide their time between these sites via a shuttle system.

Facility	Use
Intravital fluorescence microscopy laboratory #1	In vivo quantitative fluorescence microscopy measurement of hemodynamics and transport in tissues
Intravital fluorescence microscopy laboratory #2	In vivo quantitative fluorescence microscopy, including fluorescence photobleaching
Intravital fluorescence microscopy laboratory #3	In vivo quantitative fluorescence microscopy, on-line digitization of images and digital image analysis, and optical measurement of pH, pO_2, etc.
Intravital fluorescence microscopy laboratory #4	In vivo quantitative fluorescence microscopy for single vessel perfusion
Intravital fluorescence microscopy laboratory #5	In vivo two-photon laser scanning microscopy/ Animal colony
Intravital fluorescence microscopy laboratory #6	Video rate multiphoton microscopy
Intravital fluorescence microscopy laboratory #7	Multiphoton microscopy with oxygen sensing and permeability measurement capabilities
Optical frequency domain microscope suite	Imaging of tissue and blood vessels with high depth penetration based on doppler optical frequency domain technology; high frequency ultrasound imaging.
Histology facility	Serial sections, immunohistology, etc.
Pathophysiology laboratory	In vivo and ex vivo perfusion of isolated tumors and measurement of blood flow, blood pressure, interstitial fluid pressure, pO_2, etc.
Cellular biophysics laboratory	Measurement of cell deformability and dynamic adhesion; Time-lapse live cell imaging
Molecular biology laboratory	Molecular techniques
Cell culture facility	Mammalian cell culture
Tumor metabolism	Measurement of blood flow, pO_2, pH
Computing facilities	Various computer workstations, desktop and portable computers; 32 node cluster for parallel computation
Cox Animal facility	Defined flora rodents
Clinical research laboratory	Measurement in cancer patients of blood and urine markers, interstitial fluid pressure, pO_2, immunohistology, molecular and cellular studies etc.





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