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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 benefit of adding losartan to the standard of care (chemotherapy and radiation followed by surgery) in patients with locally advanced pancreatic ductal adenocarcinoma (NCT01821729). This trial provided compelling evidence in support of this emerging concept and has spawned a multi-institutional randomized clinical trial (NCT03563248) in pancreatic ductal adenocarcinoma. 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 Foundation has allowed to translated our discoveries from bench to bedside. 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 220 graduate students and post-doctoral fellows from more than 25 countries. 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 750 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 100 awards, including membership in all three branches of the US National Academies – Medicine, Engineering and Sciences, US National Academy of Inventors, US Medal of Science and more than 100 grants from various private and government agencies including the Advanced Medical Research Foundation, 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, Cholangiocarcinoma Foundation, Damon Runyon Foundation, Ellison 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, Ludwig Center at Harvard, Lustgarten Foundation, the National Institutes of Health, the National Foundation for Cancer Research, the National Science Foundation, Neuroendocrine Tumor Research Foundation, Susan Komen Foundation, United Negro College Fund, U.S. Army Breast Cancer Program, Yvonne Silverman Bequest and the Whitaker Foundation. 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 35th offering scheduled for September 21 – 24, 2020.
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.

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 750 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 three 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.
- Proposed the matrix normalization hypothesis and showed the benefit of normalizing the tumor microenvironment using angiotensin system inhibitors in pancreatic cancer in mice and in a phase II trial.
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<td>1991-</td>
<td>Humboldt Fellowships - Leunig, Dellian, Sckell</td>
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<td>1992-1996</td>
<td>Howard Hughes Fellowship - Gazit, Ang</td>
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<td>1992-1993</td>
<td>Hybritech-Lilly</td>
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<tr>
<td>1993-2000</td>
<td>Outstanding Investigator Grant, National Cancer Institute – Jain</td>
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<td>1994-1996</td>
<td>DuPont-Merck</td>
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<td>1994-1996</td>
<td>Enzon</td>
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<tr>
<td>1994-2012</td>
<td>Deutsche Forschungsgemeinschaft - Patan, Hansen-Algenstaedt, Gralla, Kunert</td>
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<tr>
<td>1994</td>
<td>Outstanding Alumnus Award, Indian Institute of Technology – Jain</td>
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<td>1995</td>
<td>Whitaker Award, Biomedical Engineering Society – Jain</td>
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<td>1996-2000</td>
<td>Whitaker Foundation (Munn)</td>
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<td>1996-1999</td>
<td>Whitaker Junior Faculty Award - Berk, Munn</td>
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<td>1996</td>
<td>Landis Award, Microcirculatory Society - Jain</td>
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<td>1996-1998</td>
<td>Whitaker BERE Fellowship - Fukumura</td>
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<td>1997-</td>
<td>National Science Foundation Fellowship – Padera, Lin, Pathak, Tong</td>
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<tr>
<td>1998-</td>
<td>National Foundation for Cancer Research</td>
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<td>1999-2000</td>
<td>Stewart Trust Award – Fukumura</td>
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<tr>
<td>1999</td>
<td>Kaplan Lecture (HMS), Berkeley Lecture (UCB) – Jain</td>
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<td>2000</td>
<td>Pharmaceutical and Bioengineering Award, American Institute of Chemical Engineers – Jain</td>
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<td>2000-2001</td>
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<td>2000-2001</td>
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<td>2000-2002</td>
<td>Mildred-Scheel-Stiftung Deutsche Krebshilfe Fellowship – Bochkorn</td>
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<td>2000-2003</td>
<td>Biotechnology Training Program Fellow – McKee</td>
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<td>2001-2002</td>
<td>Susan Komen Foundation Fellowship – Dolmans</td>
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<td>2001-2003</td>
<td>University of Copenhagen Fellowship – Junker</td>
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<td>2001-2003</td>
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<td>Honorary Fellow, Indian Institute of Chemical Engineers – Jain</td>
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<td>Netherlands America Commission for Educational Exchange Fulbright Fellowship – Hagendoorn</td>
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<td>2001-2003</td>
<td>Claffin Distinguished Scholar – Xu</td>
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<td>2001-2003</td>
<td>University of Tsukuba, Ministry of Education Science and Culture of Japan - Koike</td>
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<td>2001-2003</td>
<td>Foundation for Science and Technology of Portugal – Sousa</td>
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<td>2002</td>
<td>Bioengineering Division Award of the American Institute for Chemical Engineers – Jain</td>
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<td>2002-2006</td>
<td>The Goldhirsh Foundation</td>
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<td>2002</td>
<td>Gerritsen Award, Microcirculatory Society – Jain</td>
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<td>2002-2005</td>
<td>Cancer Research Institute – Duda</td>
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<td>2002-</td>
<td>Whitaker Foundation Graduate Fellowship – Mok</td>
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<td>2003</td>
<td>Alumni Wall of Fame, University of Delaware - Jain</td>
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<td>2003-2005</td>
<td>Emmy-Noether grant of the German Research Foundation – Winkler</td>
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<td>2003-2005</td>
<td>Susan Komen Foundation Fellowship – Tong</td>
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<td>2003-2008</td>
<td>NIH Research Career Development Award – Munn</td>
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<td>2003</td>
<td>Institute of Medicine, the National Academy of Sciences – Jain</td>
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<td>2003-2005</td>
<td>American Association for Cancer Research Career Development Award – Duda</td>
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<td>2003-2005</td>
<td>Japan Society for the Promotion of Science – Nagano</td>
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<td>2004</td>
<td>National Academy of Engineering, the National Academy of Sciences – Jain</td>
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<td>2004</td>
<td>Robert Bras Lecturer, Princess Margaret Hospital and National Cancer Institute of Canada – Jain</td>
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<td>2004-2005</td>
<td>National Defense Medical College Fellowship – Miyazaki</td>
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<td>2005-2008</td>
<td>Damon Runyon Foundation Fellowship – Lahdenranta</td>
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<td>2005</td>
<td>John S. Laughlin Lecturer, Memorial Sloan-Kettering Cancer Center, New York – Jain</td>
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<td>2005</td>
<td>AstraZeneca</td>
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<td>2005</td>
<td>French Medical Research Foundation Fellowship - LaCorre</td>
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<td>2005</td>
<td>Academic Scientist of the Year, 2005 Pharmaceutical Achievement Awards – Jain</td>
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<td>2006-2008</td>
<td>Brain Tumor Society</td>
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<td>2006-2008</td>
<td>Claffin Distinguished Award – di Tomaso</td>
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<td>2006</td>
<td>Ford Foundation Diversity Fellowship – Dawson</td>
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<td>2006-2009</td>
<td>Susan Komen Fellowship – Lacorre</td>
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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
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    Sprio 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    Sprio 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
2012    2012 Children’s Tumor Foundation – Clinical Research Award - Xu
2013    M. Gerritsen Award, Microcirculation Society - Fukumura, Duda, Munn, Jain
2013    Max Kade Foundation- Reiberger
2013    Children’s Tumor Foundation- Drug Discovery Initiative - 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    NIH R01 - Munn, Padera, Jain
2015    Secretary General, IASGO – Duda
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<tr>
<th>Year</th>
<th>Award</th>
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<td>2015</td>
<td>Eugene M. Landis Award</td>
<td>The Microcirculatory Society - Fukumura</td>
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<td>2015</td>
<td>Honorary Doctorate, Katholieke Universiteit Leuven, Belgium</td>
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<td>2015</td>
<td>Honorary Doctorate, Indian Institute of Technology (IIT), Kanpur, India</td>
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<td>2015</td>
<td>Honorary Doctorate, Duke University</td>
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<td>2015</td>
<td>Capussotti Award</td>
<td>Duda</td>
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<td>2015</td>
<td>Honoree of the One Hundred, Mass General Cancer Center</td>
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<td>LE&amp;RN/FDRS Lipedema Postdoctoral Fellowship</td>
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<td>Schrodinger Fellowship by the Austrian Science Funds</td>
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<td>2015</td>
<td>Herman-Holtheusen Award of the German Society for Radiation Oncology</td>
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<td>2015</td>
<td>Foreign Fellow, Indian National Science Academy (INSA)</td>
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<td>2015</td>
<td>Poster of Distinction Award at MGH ECOR SAC Meeting</td>
<td>Ferraro, Datta</td>
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<td>2015</td>
<td>De Beaumont Bonelli Foundation Travel Award</td>
<td>Seano</td>
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<td>2015</td>
<td>Awarde of the State Scholarship Fund by the China Scholarship Council (CSC)</td>
<td>Y. Zhao</td>
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<td>2015</td>
<td>Sprio Award</td>
<td>Padera, Xu</td>
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<td>2015</td>
<td>Merrimack Pharma SRA</td>
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<td>2015</td>
<td>Warshaw Award</td>
<td>Fukumura, Duda</td>
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<td>2015</td>
<td>Nikon Small World Competition, 5th place</td>
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<td>2015</td>
<td>SPARC SRA</td>
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<td>2015</td>
<td>North America Vascular Biology Organization Outstanding Poster Award</td>
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<td>Pierre Gilles de Gennes Fondation pour la Recherche Fellowship</td>
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<td>2015</td>
<td>Children’s Tumor Foundation Drug Discovery Award</td>
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<td>2015</td>
<td>NIH Outstanding Investigator Award</td>
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<td>2015</td>
<td>Bill and Melinda Gates Foundation Grand Challenges: New Interventions in Global Health</td>
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<td>2015</td>
<td>Ludwig Institute Grant</td>
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<td>2015</td>
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<td>2015</td>
<td>Rice University Distinguished Alumnus Award</td>
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<td>2016</td>
<td>Inductee, American Institute of Medical and Biological Engineering</td>
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<td>2016</td>
<td>Heroes of Hope Award Granara-Skerry Trust for Pancreatic Cancer Research</td>
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<td>2016</td>
<td>United States National Medal of Science (for 2013)</td>
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<td>The Kyotov University Foundation</td>
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<td>2016</td>
<td>Resource Center for Health Science (RECHS)</td>
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<td>2017</td>
<td>Lifetime Achievement Award, American Assoc. of Indian Scientists in Cancer Research</td>
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<td>2017</td>
<td>Maud Menten Lecture, University of Pittsburgh</td>
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<tr>
<td>2018</td>
<td>New England Choice Award</td>
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<td>2017</td>
<td>One of the top 1% cited researchers in Clinical Medicine</td>
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<td>2017</td>
<td>Elected to the National Academy of Inventors</td>
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<td>2017</td>
<td>Swedish Research Council Fellowship</td>
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<td>2018</td>
<td>Maud Menten Lecture, University of Pittsburgh</td>
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<td>2018</td>
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<td>Year</td>
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<td>Judah Folkman Lecture, Harvard Medical School/Boston Children’s Hospital - Jain</td>
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<td>Jeffrey M. Isner Memorial Lecture, Tufts University School of Medicine – Jain</td>
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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
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 goals 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

- 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 (Sroh et al., 2005; Allen et al., 2010; Liu et al., 2010; Chen et al., 2013), Life time imaging (Kumar et al., 2009), OFDI (Yakoc et al., 2009), (Kim et al., 2010), (Kamoun et al., 2010), video-rate MPLSM (Kirkpatrick et al., 2012),

- Developed a novel permeability 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 (Zlotocki 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, Hijnj et al., 1999).

- Discovered new mechanisms of tumor angiogenesis (Patan et al., 1996) and vascular anastomosis (Cheng et al., 2011).


- Demonstrated roles of nitric oxide (Fukumura et al., and Jain, 1998; Fukumura et al., 2000) on 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 potentiates 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-Etiene et al., 1999; Padera et al., 2004).

- Demonstrated the importance of host organ in 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).

- Demonstrated 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-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., 1999).

- Demonstrated that anti-VEGF and anti -VEGF-R2 antibodies potentiate radiation-induced short term and long term tumor control (Lee et al., 2000; Koiz 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 autochthonous 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 IP cells (Samuel et al., 2013).

- Discovered the differential transplantability of tumor stromal cells and stromal cell metastasis (Duda et al., 2004, 2010).

- Demonstrated that anti-angiogenic therapy is effective (Tong et al., 2004; Winkler et al., 2004; Kashiwagi et al., 2008; Kamoun et al., 2009; Huang et al., 2012).

- Characterized nanoparticle transport (Sroh et al., 2005) and the effect of size (Popovic et al., 2010; Chauhan et al., 2012), charge (Campbell et al., 2002; Stilianopoulos et al., 2010 & 2013; Han et al., 2013), shape (Chauhan et 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 resistance (Chae et al., 2010; Peterson et al., 2016; Kloepper et al., 2016).

- Demonstrated that CXCR4 promotes metastasis via Gr-1+ BMDC recruitment (Hiratsuka et al., 2011).

- Discovered that tumors prime metastatic “soil” by inducing focal hyperpermeability in the lungs (Hiratsuka et al., 2011).

- Determined how fluid forces and VEGF cooperate to control angiogenic sprouting (Song & Munn, 2011).

- Discovered PIGF/NRP1 as a novel therapeutic target in pediatric medulloblastoma (Snuderl et al., 2013).

- Discovered that obesity induces anti-VEGF therapy resistance via IL-6 and bFGF (Incio et al., 2018).
Discovered that obesity induces inflammation, and developed "smart" nano-particles that become smaller in size once they enter the tumor microenvironment (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).

Discovered that hyperpermeability of tumor vessels coupled with high interstitial pressure can lead to vascular stasis (Netti et al., 1996, Baish et al., 1997).

Demonsrtated that hyperpermeability in tumors (Helmlinger et al., 2000).

Discovered that hyperpermeability of tumor vessels can control permeability (Yuan et al., 1994a, 1995; Helmlinger 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 (Hobs et al., 1998).

Demonstrated that the gaps between endothelial cells cause hyperpermeability in tumors (Hashizume et al., 2000).

Demonstrated the effect of PlGF and VEGF on the hydraulic conductivity of endothelium in vitro (Dull et al, 2001).

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).

Delineated the signaling pathways for low pH regulation (Fukumura et al, 1997b).

Found that decompressing vessels with angiotensin inhibition can enhance oxygen delivery to tumors (Chauhan et al., 2013).

Demonsrtated 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 vessel hyperpermeability can influence tumor microcirculation in the rabbit ear chamber and mouse dorsal chamber (Martin and Jain, 1993, Martin and Jain, 1994, Dellian et al., 1996b).

Determined that vascular normalization can enhance the penetration of small but not large nanomedicines in tumors (Chauhan et al., 2012).

Delineated the mechanisms of low pH in tumors (Helmlinger et al., 2002).

Demonstrated a lack of universal correlation between pO2 and IFP (Boucher et al., 1995).

Discovered that HIF-1α deletion leads to lower VEGF expression, angiogenesis and oxygenation, yet the tumors grow more rapidly (Carmeliet et al., 1998), and HIF1α (-/-) 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).

Discovered that obesity induces inflammation, desmoplasia and resistance to anti-angiogenic therapy in breast cancer via IL-6 and bFGF (Incio et al, 2018) and chemotherapy in pancreatic cancer via IL-1 (Incio et al., 2016).
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, 1996a, Johnson et al., 1996b, Pluen et al., 1995).

- 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 (Montalvo-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 (Hagedoorn 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).

- Showed that MRSA infections permanently impair lymphatic pumping by killing lymphatic muscle cells (Jones et al., 2018).

- Showed that lymph node metastasis can invade lymph node blood vessels, escape the lymph node and colonize distant metastatic sites (Pereira et al., 2018).

- Showed that tumor draining lymphatic vessels have impaired pumping (Liao et al, 2019)
RESEARCH HIGHLIGHTS

- 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, Mouton 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) and anti-VEGF therapy and obesity induces ECM deposition and mechanical stress that compress blood vessels (Rahbari et al, 2016; Incio et al, 2015 & 2016).
- Demonstrated 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) and targeting fibroblasts by angiotensin receptor blocker (ARB) significantly improved pancreatic cancer surgery (Liu et al, 2017; Murphy et al, 2018).
**RESEARCH HIGHLIGHTS**

- 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 haptons, 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).


- 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.
- 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) (Zhu et al., 2009).
- 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).
- 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).
- Discovered that the anti-VEGFR2 agent cabozantinib has immunomodulatory effects in breast cancer patients (Tolaney et al., 2017).
- Demonstrated that adding losartan – to normalize the tumor matrix – to chemoradiotherapy was associated with high complete resection rates in locally advanced pancreatic ductal adenocarcinoma patients (Murphy et al., 2018).
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

Reengineering the Tumor Microenvironment to Improve Cancer Treatment: “Bench to Bedside” & Back

A solid tumor is an organ composed of cancer cells and host stromal cells, which are nourished by the vasculature and embedded in an extracellular matrix. The interactions among these cells, the surrounding matrix, and the local cellular microenvironment fuel tumor progression, and affect the tumor’s response to various therapies. Blood and lymphatic vessels also serve as conduits for metastatic spread. The overarching 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 growth, metastasis and treatment, and 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. We also discovered that cancer cells co-opt the host stromal cells and entice them to produce pro- and anti-growth factors.

Our work has revealed that the abnormal vascular and extravascular compartments in solid tumors often thwart the effectiveness of both conventional and novel therapies, including immunotherapy. Our laboratory is most celebrated for a new hypothesis that “normalizing” the abnormal tumor vasculature and matrix can 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 have guided the development of novel diagnostic and therapeutic strategies.

Selected Publications

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

The rich fibrillar collagen content – associated with tumor desmplasia – is a significant barrier to drug delivery in tumors. We found that the angiotensin system inhibitor (ASI) losartan produces a dose-dependent reduction in stromal collagen in several tumor models including pancreatic ductal adenocarcinoma (PDAC) in mice. Losartan also improved vascular perfusion, the distribution and therapeutic efficacy of Doxil and small cytotoxic agents in PDAC and breast cancer models. In a recent retrospective study we found that the chronic use of ASI is independently associated with longer overall survival in non-metastatic PDAC patients. Unbiased gene expression profiling suggested that the improved survival associated with ASI therapy in PDAC patients might be due to inhibition of tumor progression and enhanced anti-tumor immunity. Based on our experimental results, we initiated a clinical trial at Massachusetts General Hospital to determine in patients with locally-advanced PDAC whether losartan improves the efficacy of the drug cocktail FOLFIRINOX. The published results of the FOLFIRINOX-losartan trial indicate that the addition of losartan is associated with a surgical resection rate of 69.4% and R0 resection of 61%. The median OS for all patients was 31.4 months.

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 (OV) is safe and leads to virus delivery / infections in tumor lesions. Nevertheless, the i.v. delivery of therapeutic doses of OV 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 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 OV (Han, submitted). 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 linked to the disruption of adherens 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 OV. Ganetespib combined with a relatively low dose of OV 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 β1 is required for the close interaction between collagen fibers and TAFs. While MMPs affect cancer cells and TAF migration, the relative stiffness of the tumor matrix can also influence cancer cell migration. We demonstrated that the stiffness of collagen fibers restricts the RhoA-dependent amoeboid movement of cancer cells. In another study we found that TAFs isolated from human breast cancer samples enhance RhoA/ROCK signaling and amoeboid movement. The crosstalk between TAFs 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 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 invasation. 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.

Selected Publications

Biliary-Pancreatic (HBP) Malignancies and Metastatic Diseases

The research of Dr. Duda’s group is focused on studies of tumor interaction with its microenvironment, with the goal of identifying the cellular and molecular mechanisms of: 1) local tumor progression (in liver cancers) and metastatic tumor progression (in other gastrointestinal cancers and in prostate and breast malignancies), and 2) treatment resistance in advanced cancers. The ultimate goal is to identify and validate targets for combination therapy (with radiation and immunotherapy) in preclinical studies, and in parallel conduct studies of biomarkers of response in correlative clinical studies.

This research is currently supported by grants from the US National Cancer Institute, by The Samuel Singer Brown Fund for Pancreatic Ductal Adenocarcinoma Research, The Neuroendocrine Tumor Research Foundation and by partnerships with the Industry (Bayer, Bristol Myers Squibb, Exelixis, and Leap Tx).

He has authored over 220 publications so far, of which 125 are original reports, including articles in Nature, Nature Genetics, Nature Medicine, Cell, Cancer Cell, Cancer Discovery, Science Translational Medicine, PNAS, JNCI, and Journal of Clinical Oncology. He has been invited to present his results at over 200 local, national and international meetings, including Grand Rounds, Plenary Talks and Keynote Lectures. For his work, Dr. Duda received several awards, including from the American Association for Cancer Research, Cancer Research Institute, International Association of Surgeons, Gastroenterologists and Oncologists (IASGO), MGH and the Granara-Skerry Trust for Pancreatic Cancer Research. He is an Honorary Member of the Academy of Medical Sciences of Romania since 2012.

Dr. Duda obtained his DMD from the University of Medicine Iasi, Romania in 1993, and earned a PhD in Medical Sciences (Gastrointestinal Surgery) from Tohoku University Graduate School of Medicine, Sendai, Japan in 2001. After graduation, he pursued postdoctoral training with Professor Rakesh K. Jain in the Steele Laboratories for Tumor Biology, Department of Radiation Oncology, Massachusetts General Hospital (MGH) and Harvard Medical School in Boston. He became a Junior Faculty member (Instructor) in 2004, and then rose through the ranks to Full Investigator at MGH Research Institute in 2016 and Associate Professor of Tumor Biology (Radiation Oncology) at Harvard Medical School in 2012. In 2016, he was appointed as the Director of Translational Research in Gastrointestinal Radiation Oncology at MGH. He has been active internationally and is currently serving as the Head of the Cancer Research Section (since 2013) and Secretary General (since 2015) of IASGO. He is a member of the AASLD Liver Fibrosis Special Interest Group. He has also been serving as a panel member for multiple scientific expert/grant review meetings worldwide since 2009, including as a permanent member of the US NCI DMP, ACS TBG, and Belgium FWO Med4 sections (chair).

Selected Publications


Angiogenesis and Tumor Microenvironment

I have three decades of research experience and teaching in the areas of vascular biology and tumor microenvironment (TME). To this end, I have been...
developing and utilizing state of the art imaging techniques and animal models which led to the discoveries summarize below.

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. We also showed that stromal cells in the primary tumor travel with tumor cells and facilitate survival and growth of metastatic tumors. Controlling tumor-host interaction is a promising approach to facilitate tumor treatment. For example, dual blockade of angiopoietin 2 and vascular endothelial growth factor signaling can normalize tumor vasculature, reprogram immune cells and prolong survival in glioblastoma.

Role of obesity in angiogenesis, tumor growth and treatments.

Obesity is world-wide pandemic causing significant health problems. We first focused on the role of angiogenesis in obesity and discovered provocative reciprocal regulation of adipogenesis and angiogenesis. We then showed that anti-VEGF therapy reduces body weight gain in diet-induced obesity model. Subsequently, we have been studying the underlying mechanisms of obesity-induced aggravation of pancreatic and breast cancers. We found IL-1β-mediating reciprocal activation among cancer associated adipocytes, fibroblasts and myeloid cells that worsens desmoplasia, hypoxia, immunosuppression, and progression, metastasis and treatment resistance of pancreatic cancers. We also found IL-6 and bFGF mediate anti-VEGF therapy resistance in obesity in both breast cancer preclinical studies and clinical trials of breast cancer patients.

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. Furthermore, NO mediates angiogenesis and vessel maturation predominantly through endothelial NO synthase. We also found that NO mediates lymph-angiogenesis, lymphatic function and metastasis. On the other hand, we also found that tumor cell-derived NO dysrupts perivascular NO gradients resulting in abnormal structure and function of tumor vasculature. Hence, we have been developing novel strategies for tumor vascular normalization by targeting tumor cell NO production to restore perivascular NO gradients and improve immune microenvironment and response to immunotherapy.

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.

Engineering blood vessels

A major limitation of tissue engineering is the lack of functional blood and lymph vessels. We established, for the first time, a model of tissue engineered blood vessels that generates durable functional blood vessels from endothelial cells and perivascular cell precursor cells in vivo which last the rest of host animal life. Using this tissue engineered blood vessel model, we further demonstrated successful generation of endothelial cells from human ES cells and cord blood and peripheral blood-derived progenitor cells, perivascular cells from human bone marrow derived mesenchymal stem cells, and functional blood vessels from them. Finally, 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.

Selected Publications


Cancer Metastasis

Our research focuses on mechanisms governing the development of brain tumors, with primary emphasis on the identification and characterization of novel tumor suppressor 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 responsible 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, 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.

Selected Publications

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

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 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 rhabdomyosarcomas, from our spontaneous nonthymic tumors, including 8 myoepitheliomas and 3 rhabdomyosarcomas, 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 genotutbiotic mice, as well as changes their pathological patterns, and (b) spontaneous tumors developed in 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.

Selected Publications

Tumor Mechanobiology and Vascular Physiology

The Munn Laboratory focuses on mechanobiology of cancer and the vascular systems:

**Lymphatic Pumping**
Flow of fluid within the lymphatic system is central to many aspects of physiology, including fluid homeostasis and immune function, and poor lymphatic drainage results in significant morbidity in millions of patients each year. We are investigating the mechanisms of lymphatic pumping, considering the nitric oxide and calcium dynamics driven by mechanobiological mechanisms.

**Vascular Anastomosis**
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, PIGF 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.

**Angiogenic Sprouting**
During angiogenesis, endothelial 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.

**Mathematical Modeling**
With sufficient understanding of the underlying mechanisms, mathematical models can be assembled to validate existing hypotheses and generate new ones.

**Selected Publications**
The lymphatic system in disease processes and cancer progression

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, lymphatic vessels 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 set 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. Currently, there are no FDA approved drugs indicated to alter lymphatic function, which presents an important opportunity to develop such drugs for the first curative treatments for lymphedema and other lymphatic related disorders.

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. We have also shown that cancer cells from lymph node metastases can invade lymph node blood vessels, escape the lymph node and colonize distant metastatic sites. Thus, lymph node metastases can be a source of distant metastases. 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 have also shown the s. aureus infections permanently impair lymphatic pumping and flow by destruction of lymphatic muscle cells. We have identified a bacterial regulatory element in s. aureus that controls the toxins responsible for this lymphatic muscle cell death. We are now developing drug candidates to protect lymphatic muscle cells in order to preserve lymphatic function during and after infections, which will prevent recurrent infections and lymphedema.

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.

Selected Publications

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-glycoprotein (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. Furthermore, 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.

Selected Publications

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Original Articles


1993 Publications

Original Articles


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58
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2016 Publications


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Original articles


2017 Publications


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# RESEARCH TEAM

<table>
<thead>
<tr>
<th><strong>Professor</strong></th>
<th>Rakesh K. Jain</th>
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</table>
| **Associate Professors** | Yves Boucher  
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Lance L. Munn  
Tim Padera |
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Yao Sun  
Limeng Wu  
Wei Yang  
Weining Yang  
Changli Yue  
Yanxia Zhao |
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| **Graduate Students** | Ashwin Kumar  
Jun Ren  
William Ho  
Jan Willem van Wijnenbergen  
Mohammad Nikmaneshi |
| **Fellows** | Patrik Andersson  
Zohreh Amoozger  
Jiang Chen  
Sampurna Chaterjee  
Yoon Sun Choi  
Meenal Datta  
Gino Ferraro  
Lei Gao  
Koetsu Inoue  
Kazunichi Kawakubo  
Hiroto Kikuchi  
Sergey Kozin  
Shanmugarajan Krishnan  
Pinji Lei  
Huabing Li  
Chong Liu  
Aya Matsui  
Bhushan Patel  
Ethel Perreira  
Jesica Posada  
Nick (Xiaoling) Qi  
Jun Ren |
| **Technical Assistants** | Aurea Aguasvivas  
Mark Duquette  
Ya Li (Sandy) Quan  
Julia Kahn  
Anna Khachatryan  
Brigido Lopez  
YanFang Lu  
Nghia Pham  
Sylvie Roberge  
Carolyn Smith  
Tsion Tale  
Penny Tale  
Rikcy Yun |
| **Administrative support** | Zeina Chaptini  
Elizabeth Garzon |
In September 1991, we started with a small team of six people, and we have since grown to approximately 65 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 postgraduate students - several of them have become leaders in academia, government and industry.
## ALUMNI

### Assistant Professors
- Robert J. Melder 1989 - 98
- Fan Yuan 1990 - 96
- David Berk 1992 - 98
- E. diTomaso 1998 - 09

### Instructors
- Intae Lee 1991 - 94
- Ping Jiang 1997 - 98
- Kevin Burton 1999 - 2001

### Fellows
- Cindy Znati 1990 - 95
- Michael Leunig 1991 - 93
- Robert Zlotekci 1992 - 93
- Paul Kristjansen 1992 - 94
- Anders Leu 1993 - 94
- Manfred Stohrer 1993 - 94
- Shige Yamada 1993 - 94
- Marc Dellian 1993 - 95
- Mutsumi Nozue 1993 - 95
- Shigeru Tanda 1994 - 96
- Mit Endo 1994 - 97
- Gabriel Helmlinger 1994 - 97
- Paolo Netti 1994 - 97
- Sybil Patan 1994 - 99
- Stuart Frederich 1996 - 97
- Axel Sckell 1996 - 97
- Lance Wilsey 1996 - 97
- Genevieve Griffon 1996 - 98
- Wayne Monsky 1996 - 98
- Takeshi Gohongi 1997 - 00
- Alain Pluen 1997 - 00
- Jin Yuan 1997 - 00
- Nils Hansen 1997 - 98
- Keiichi Ohtaka 1997 - 98
- Marc Heijn 1997 - 99
- Chang Geol Lee 1997 - 99
- Kyung Ran Park 1997 - 99
- Saroja Ramanujan 1998 - 00
- Yoshikazu Tsuzuki 1998 - 01
- Chieko Koike 1998 - 00
- Ananth Kadambi 1998 - 01
- Yong Chang 1998 - 00
- Chae - Ok Yun 1998 - 00
- Randal Dull 1998 - 99
- Sergey Kozin 1998 - 15
- Yotaro Izumi 1999 - 02
- Vincent Moutardier 1999 - 00
- Carla Mouta - Carreira 1999 - 01
- Robert Campbell 1999 - 02
- Edward Brown 1999 - 05
- Brenda Fenton 2000 - 01
- Oliver Gralla 2000 - 01
- Cristiano Migliorini 2000 - 01
- Akira Ushiyama 2000 - 01
- Xiaoye Wang 2000 - 01
- Maximilian Bockhorn 2000 - 02
- Dennis Dolmans 2000 - 02
- Neil Forbes 2000 - 02
- Tiina Roose 2001 - 02
- Naoto Koike 2001 - 03
- George Alexandrakis 2001 - 04
- Zoe Demou 2001 - 04
- Nachide Isaka 2002 - 04
- Mark Stroh 2002 - 04
- Chenghai Sun 2002 - 05
- Patrick Au 2002 - 09
- Frank Winkler 2003 - 04
- Jeroen Hagendoorn 2003 - 05
- Mitsutomo Kohno 2003 - 05
- Michael Booth 2003 - 06
- Tohru Hoshida 2003 - 06
- Satoshi Kashiwagi 2003 - 06
- Mai Luong 2003 - 07
- Aaron Mulivor 2003 - 07
- Sung Suk Chae 2004 - 10
- Junichi Miyazaki 2004 - 05
- Michael Dupin 2004 - 07
- Aaron Mulivor 2004 - 07
- Greg Nelson 2004 - 07
- Jean Yannis Perentes 2004 - 07
- Satoshi Nagano 2004 - 09
- Cimona Hinton 2005
- Carsten Ley 2005
- Delphine Lacorre 2005 - 11
- Kevin Kozak 2005 - 07
- Carsten Ley 2005 - 07
- Michelle Dawson 2005 - 08
- Johanna Lahdennranta 2005 - 08
- Mai Luong 2005 - 08
- Gang Cheng 2005 - 09
- Walid Kamoun 2006 - 11
- Annette Pieters 2006 - 10
- Kevin Kozak 2006 - 07
- J. Alex Tyrrell 2006 - 08
- Angera Kuo 2006 - 09
- Euiheon Chung 2007 - 10
- Sachie Nakamura 2007 - 10
- Hiroshi Yamashita 2007 - 09
- Kosuke Tsukada 2007 - 09
- Andus Wong 2007 - 09
- Shan Liao 2007 - 13
- Rekha Samuel 2008 - 11
- T. Stylianopoulos 2008 - 10
- Ned Kirkpatrick 2008 - 13
- Matija Snuderl 2008 - 12
- Jonathan Song 2008-14
- Han - Sing Jeong 2009 - 11
- Termitope Sondunke 2009 - 10
- Jayeeta Bhaumik 2010 - 11
- Christian Kurtner 2010-15
- David Kodack 2010-14
- Christina Kesler 2010 - 13
- Becky Chen 2010 - 13
- Christine Lu-Emerson 2010 - 12
- Janet Tse 2010 - 11
- Ana Batista 2010 - 15
- Robin Amlung 2011-15
- Lars Riedemann 2011-13
- Eleanor Ager 2011-13
- Despina Bazou 2011-16
- Tatiana Demidova-Rice 2011-13
- Nuh Rahbari 2011-13
- Gabriel Gruionu 2011-15
- Julien Daubiac 2011-15
- Rouxu Dou 2012-15
- Vikash Chauhan 2012-15
- Nir Maimon 2012-19
- Mark Badeaux 2012-17
- Dennis Jones 2012-18
- Echoe Bouta 2012-17
- Jennie Taylor 2012-14
- Trupti Vardam 2012-15
- Vera Verbugen 2012-15
- Xiaoxing Han 2012-15
- Jonas Kloeppe 2012-16
- Daniel Schanne 2013-17
- Tai Hato 2013-16
- Giorgio Seano 2013-18
- Rosa Ng 2013-18
- Shuang Yan 2014-15
- Ross Kitahara 2014-17
- Sen Li 2014-16
- Hadi Nia 2014-18
- Louis Larrouquere 2015-17
- Yingchao Zhao 2015-16
<table>
<thead>
<tr>
<th>Name</th>
<th>Years</th>
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<tr>
<td>Eelco Meijer</td>
<td>2015-17</td>
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<tr>
<td>Yuhui Zhao</td>
<td>2015-17</td>
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<td>Matthias Pinter</td>
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<td>Ivy Chen</td>
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<td>Mitrajit Ghosh</td>
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<td>Emilie Manessier</td>
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<td>Kohei Shigeta</td>
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<td>Kosuke Kawaguchu</td>
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<td>Som Nath Pandey</td>
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<td>Christian Brekken</td>
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<td>Vikash Chauhan</td>
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<td>Benjamin Diop-Frimpong</td>
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<td>Ming - Zer Poh</td>
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<td>Jieqion (Jane) Liu</td>
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<td>John Martin</td>
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<td>Kamila Naxterova</td>
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<td>Elisabeth Niemeyer</td>
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<td>Koen Marit</td>
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<td>Rakesh Ramjawan</td>
<td>2012-18</td>
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<td>Nisha Gupta</td>
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<td>Li Chong</td>
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<td>Meenal Datta</td>
<td>2013-18</td>
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<td>Eric Kaufman</td>
<td>1988-92</td>
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<td>Patrick Yoon</td>
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<td>Peter Khalifah</td>
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<td>Valerie Verdier</td>
<td>1995-96</td>
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<tr>
<td>James Baish</td>
<td>1994, 2013, 2017</td>
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<tr>
<td>Catharina Davies</td>
<td>1997-98</td>
</tr>
<tr>
<td>John Tarbell</td>
<td>1997-98</td>
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<tr>
<td>Donald Buerk</td>
<td>1998-99</td>
</tr>
<tr>
<td>Robert Feil</td>
<td>2012-13</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Facility</th>
<th>Use</th>
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<tbody>
<tr>
<td>Intravital fluorescence microscopy laboratory #1</td>
<td>In vivo quantitative fluorescence microscopy measurement of hemodynamics and transport in tissues</td>
</tr>
<tr>
<td>Intravital fluorescence microscopy laboratory #2</td>
<td>In vivo quantitative fluorescence microscopy, including fluorescence photobleaching</td>
</tr>
<tr>
<td>Intravital fluorescence microscopy laboratory #3</td>
<td>In vivo quantitative fluorescence microscopy, on-line digitization of images and digital image analysis, and optical measurement of pH, pO(_2), etc.</td>
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<tr>
<td>Intravital fluorescence microscopy laboratory #4</td>
<td>In vivo quantitative fluorescence microscopy for single vessel perfusion</td>
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<tr>
<td>Intravital fluorescence microscopy laboratory #5</td>
<td>In vivo two-photon laser scanning microscopy/ Animal colony</td>
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<td>Intravital fluorescence microscopy laboratory #6</td>
<td>Video rate multiphoton microscopy</td>
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<tr>
<td>Intravital fluorescence microscopy laboratory #7</td>
<td>Multiphoton microscopy with oxygen sensing and permeability measurement capabilities</td>
</tr>
<tr>
<td>Optical frequency domain microscope suite</td>
<td>Imaging of tissue and blood vessels with high depth penetration base on doppler optical frequency domain technology; high frequency ultrasound imaging.</td>
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<tr>
<td>Histology facility</td>
<td>Serial sections, immunohistology, etc.</td>
</tr>
<tr>
<td>Pathophysiology laboratory</td>
<td>In vivo and ex vivo perfusion of isolated tumors and measurement of blood flow, blood pressure, interstitial fluid pressure, pO(_2), etc.</td>
</tr>
<tr>
<td>Cellular biophysics laboratory</td>
<td>Measurement of cell deformability and dynamic adhesion; Time-lapse live cell imaging</td>
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<tr>
<td>Molecular biology laboratory</td>
<td>Molecular techniques</td>
</tr>
<tr>
<td>Cell culture facility</td>
<td>Mammalian cell culture</td>
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<tr>
<td>Tumor metabolism</td>
<td>Measurement of blood flow, pO(_2), pH</td>
</tr>
<tr>
<td>Computing facilities</td>
<td>Various computer workstations, desktop and portable computers; 32 node cluster for parallel computation</td>
</tr>
<tr>
<td>Cox Animal facility</td>
<td>Gnotobiotic mice (33 strains)</td>
</tr>
<tr>
<td>Clinical research laboratory</td>
<td>Measurement in cancer patients of blood and urine markers, interstitial fluid pressure, pO(_2), immunohistology, molecular and cellular studies etc</td>
</tr>
</tbody>
</table>

RESOURCES AND ENVIRONMENT