

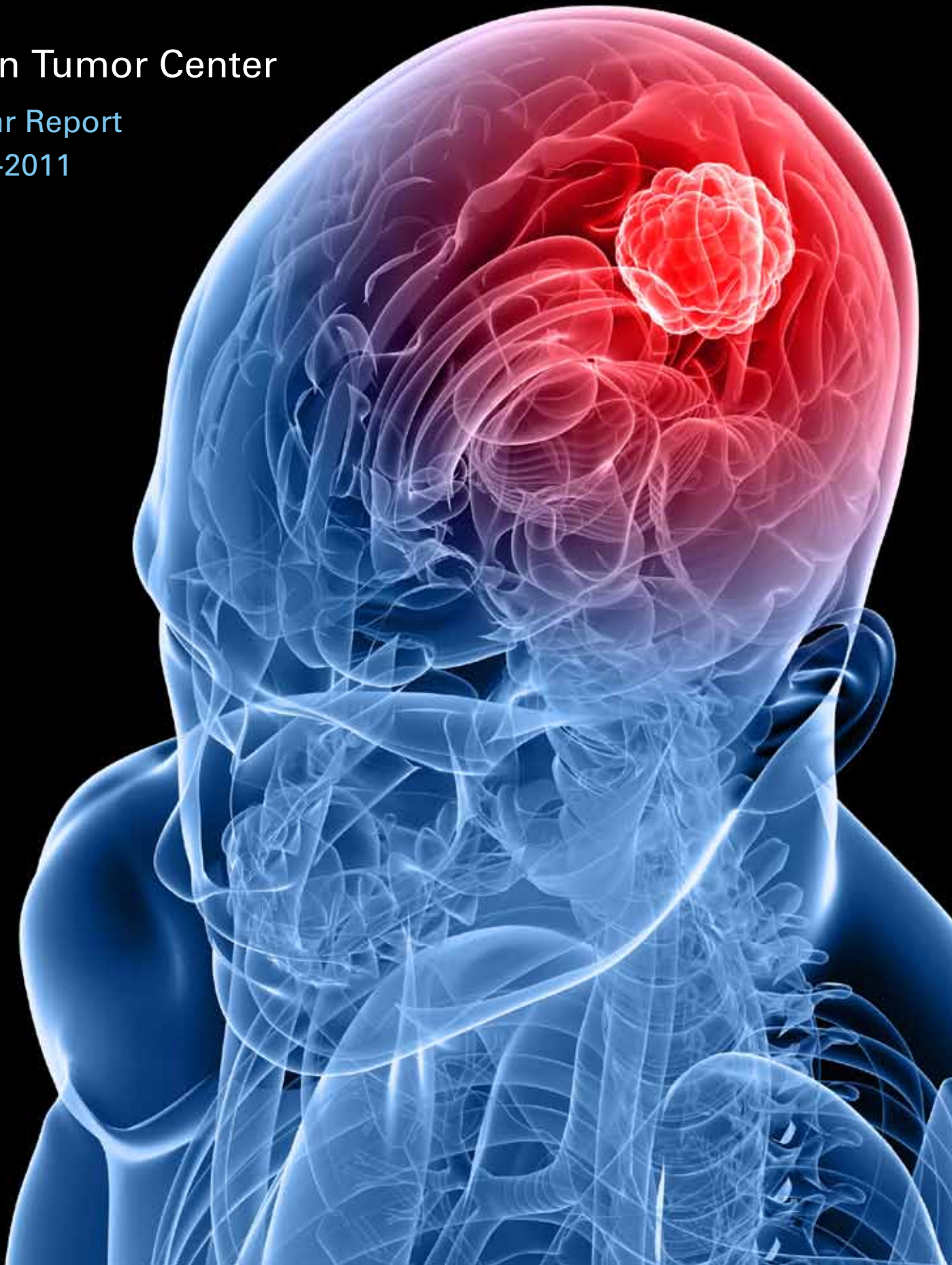


Memorial Sloan-Kettering  
Cancer Center

# Brain Tumor Center

5-Year Report

2007-2011







<b>Faculty</b>	<b>2</b>
<b>BTC 5-Year Accomplishments</b>	<b>5</b>
<b>Metrics</b>	<b>15</b>
<b>Progressive Clinical Care</b>	<b>25</b>
<b>Making an Appointment</b>	<b>28</b>
<b>Molecular Neuro-oncology</b>	<b>35</b>
<b>BTC Publications</b>	<b>46</b>

## NEUROLOGY



Lisa M. DeAngelis, MD



Edward K. Avila, DO



Ronald G. Blasberg, MD



Xi Chen, MD, PhD



Milan G. Chheda, MD



Denise D. Correa, PhD



Kevin C. De Braganca, MD



Kathleen M. Foley, MD



Igor T. Gavrilovic, MD



Christian Grommes, MD



Thomas J. Kaley, MD



Ingo K. Mellinger, MD



Craig P. Nolan, MD



Antonio M. Omuro, MD



Gavril W. Pasternak, MD, PhD



Elena Pentsova, MD



Jerome B. Posner, MD



Sonia K. Sandhu, DO



Jonas M. Sokolof, DO



Michael D. Stubblefield, MD

## NEUROSURGERY



Philip H. Gutin, MD



Mark H. Bilsky, MD



Cameron W. Brennan, MD



Jeffrey P. Greenfield, MD, PhD



Eric C. Holland, MD, PhD



Samuel H. Selesnick, MD, FACS



Mark M. Souweidane, MD



Viviane Tabar, MD

## RADIATION ONCOLOGY



Kathryn Beal, MD



Timothy A. Chan, MD, PhD



Brett W. Cox, MD



Shyam S. Rao, MD, PhD



Melissa R. Remis, MD



Yoshiya Yamada, MD



Suzanne L. Wolden, MD, FACP

## PEDIATRIC NEURO-ONCOLOGY



Ira J. Dunkel, MD



Stephen W. Gilheaney, MD, MMS



Yasmin Khakoo, MD



Kim Kramer, MD



David C. Lyden, MD, PhD

## NEURORADIOLOGY



Hedvig Hricak, MD, PhD



Michelle S. Bradbury, MD, PhD



Sofia S. Haque, MD



Vaios Hatzoglou, MD



Andrei I. Holodny, MD



Sasan Karimi, MD



Moritz F. Kircher, MD, PhD



George Krol, MD



Eric Lis, MD



John Lyo, MD



Hilda E. Stambuk, MD



Robert J. Young, MD

TREATING PHYSICIANS

BRAIN  
CEN

DIAGNOSTIC &

## MOLECULAR PHARMACOLOGY & CHEMISTRY



Luca Cartegni, PhD



Hakim Djaballah, PhD



Michael R. McDevitt,  
PhD, ME



Stephen Nimer, MD



Gavril W. Pasternak,  
MD, PhD



Neal Rosen, MD, PhD

## DEVELOPMENTAL BIOLOGY



Alexandra Joyner, PhD



Songhai Shi, PhD



Lorenz Studer, MD

## CANCER BIOLOGY & GENETICS



Joan Massagué, PhD



Robert Benezra, PhD



Eric C. Holland, MD, PhD



Johanna Joyce, PhD



Craig B. Thompson, MD

## MOLECULAR BIOLOGY



Andrew Koff, PhD



John Petrini, PhD

## CELL BIOLOGY



Xuejun Jiang, PhD



Marilyn Resh, PhD

## NEUROPATHOLOGY



Jason T. Huse, MD, PhD



Marc K. Rosenblum, MD

## HUMAN ONCOLOGY & PATHOGENESIS PROGRAM



Charles L. Sawyers, MD



Cameron W. Brennan, MD



Timothy A. Chan,  
MD, PhD



Jason T. Huse, MD, PhD



Ingo K. Mellinghoff, MD

TUMOR  
TER

BASIC & TRANSLATIONAL  
RESEARCH

SUPPORTIVE  
CARE

## COMPUTATIONAL BIOLOGY



Chris Sander, PhD

## SURGERY



Bhuvanesh Singh, MD,  
PhD, FACS

## RESEARCH STAFF



Desert Horse-Grant



Raquel Sanchez



Kara Colevas



Amanda Conlon

## PSYCHIATRY & BEHAVIORAL SCIENCES



Tim A. Ahles, PhD



William S. Breitbart, MD



Chirstine Ferreira



Mahitha Vallurupalli



Jianan Zhang

## EPIDEMIOLOGY & BIostatISTICS



Jonine Bernstein, PhD



Sara Olson, PhD



Katherine Panageas, DrPH

## ANESTHESIOLOGY & CRITICAL CARE MEDICINE



Amitabh Gulati, MD



Vinay Puttanniah, MD



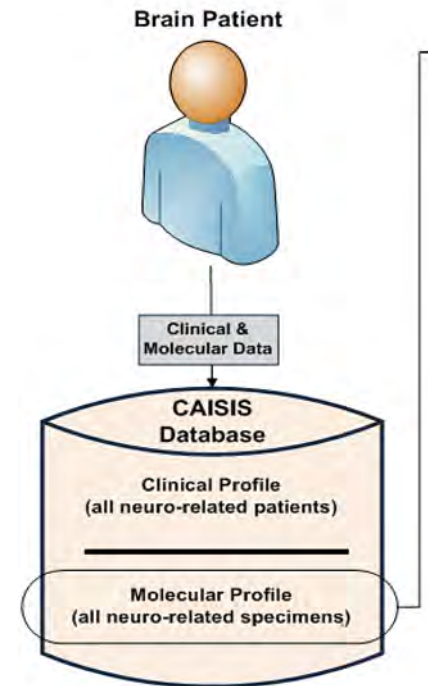
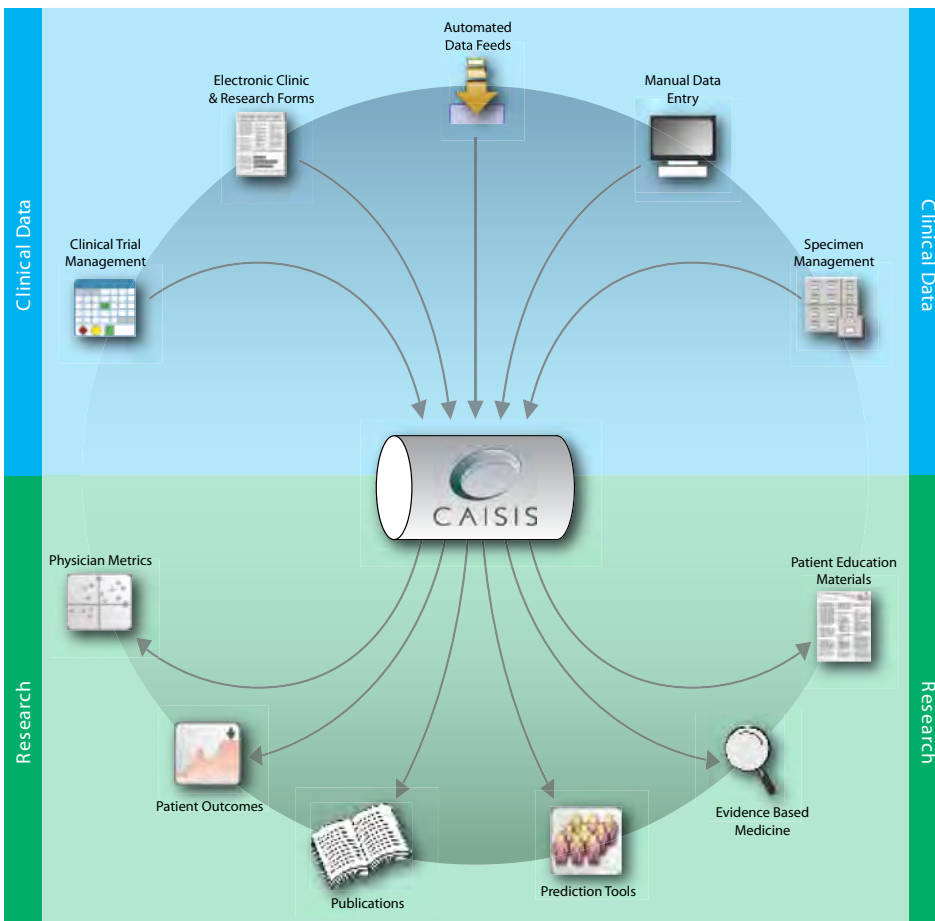


# BTC 5-Year Accomplishments

## BTC Tumor Bank/CAISIS Database

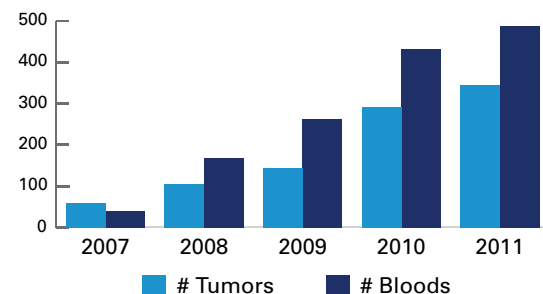
Creating a centralized Brain Tumor Center allows faculty and leadership to follow metrics & celebrate milestones. Faculty are diligently working on innovative scientific advancements, clinical trials and the molecular profiling of tumors. The development of the Brain Tumor Tissue and Serum Bank paired with a fully annotated, customized clinical database is the backbone of much of the current and future work of the BTC. Over 1,000 brain tumor specimens have been collected to date, which largely include corresponding blood samples, along with the full

history of every brain patient who has come to MSKCC in the past four years. Investigational molecular tumor profiling is fed into our database and joined with standard molecular tests done by clinical pathology. **Clinical data on all 2007-2011 MSKCC brain patients has been captured and all 2010-2011 consented GBM patients have molecularly profiled tumor data captured. Together, this dataset is invaluable for driving translational research and laying the groundwork for personalized, targeted therapy of brain tumors stratified by subtypes.**



BTC Patients with Full Clinical Data Captured 2007-2011	# Unique Patients	# Unique Patient Tumors
Glioma Patients	1946	719
Meningothelial Tumor Patients	304	134
Brain Metastasis Patients	234	195
PCNSL Patients	187	11
Pituitary Adenoma Patients	273	3
Other	708	71

Banked Brain Biospecimens, by Year

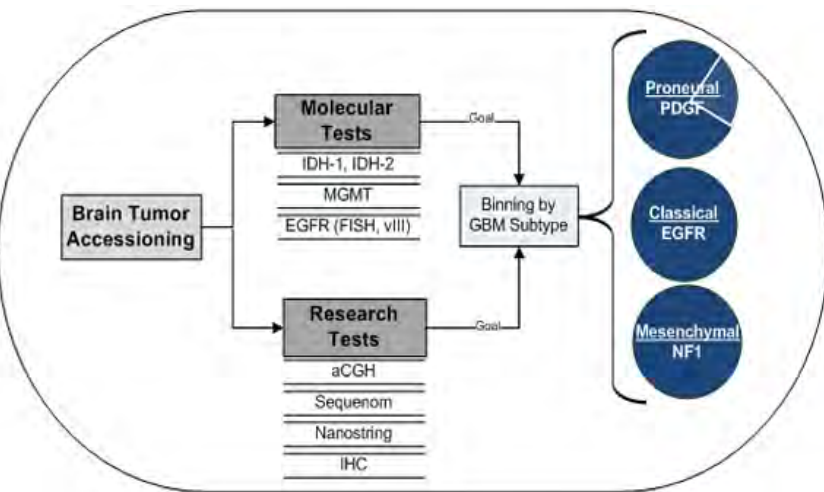




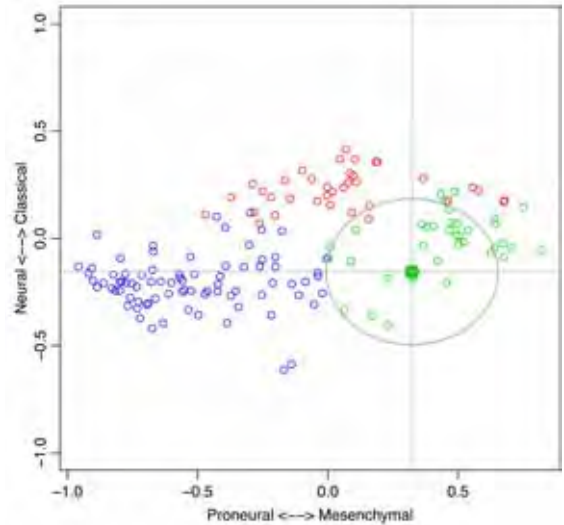
## Molecular Profiling of GBM Tumors

Our research molecular profiling panel includes a number of cutting-edge tests developed recently in the laboratories of BTC faculty members **Jason Huse, Cameron Brennan,** and **Ingo Mellinghoff.** The tests are designed to simultaneously profile an array of biomarkers that recent research indicates are of likely importance to both prognosticate disease outcome and stratify patients into treatment-relevant subgroups. We have now applied our

panel to almost 90 samples, which is functioning in real time, profiling specimens as they are removed from patients undergoing brain surgery at MSKCC. In addition, automated computational pipelines have been developed internally to generate refined reports harboring already-interpreted data. We are now poised to greatly advance our capability as an institution to perform molecularly driven trials.



Tumor Banking, molecular testing and binning of GBM tumors



Neural (red), Classical (green), Mesenchymal (blue)

Proneural Plot pinpointing one GBM tumor stratified against all 2011 tumors molecularly profiled in BTC Bank

- Live link to research molecular profiling
- Fully de-identified (BTC bank number)
- Common repository for molecular data

Sample: TB525

ACGH Summary: **\*\*EGFR\* -PIEN\***

chrom	chromStart	chromEnd	name	transcript	strand	ch	min	max	icna
chr7	53070842	53072111	DKFZp564N2472	NM_182595	+	7	1.5752	1.5752	FALSE
chr7	54577512	54604442	VSTM2A	NM_182546	+	7	1.5752	1.5752	FALSE
chr7	54787434	54794433	SEC61G	NM_001012456	-	7	2.6503	2.6503	FALSE
chr7	55054218	55242524	EGFR	NM_201283	+	7	2.0089	2.7664	TRUE
chr7	55400634	55468927	LANCL2	NM_018697	+	7	2.476	2.476	FALSE
chr7	55505800	55607694	ECOP	NM_030796	-	7	2.476	2.476	FALSE
chr7	55716261	55724488	FKBP9L	NM_182827	-	7	2.476	2.476	FALSE
chr7	55828730	55897976	SEPT14	NM_207366	-	7	2.476	2.476	FALSE
chr7	55947824	55975927	ZNF713	NM_182633	+	7	1.1909	2.476	TRUE
chr7	56099410	56115858	SUMF2	NM_001042468	+	7	1.1909	2.1636	TRUE
chr7	56116168	56128192	DHXC1	NM_002912	-	7	2.1636	2.1636	FALSE
chr20	149	149						0562	TRUE

Created by Dr. Cameron Brennan

Example: list all amplified/deleted genes

## BTC Grant Winners

2011



Top: E. Bazzoli, MD, M. Evans, PhD, A. Fabius, PhD  
Bottom: J. Huse, MD, PhD, M. Kircher, MD, PhD, B. Oldrini, PhD

2010



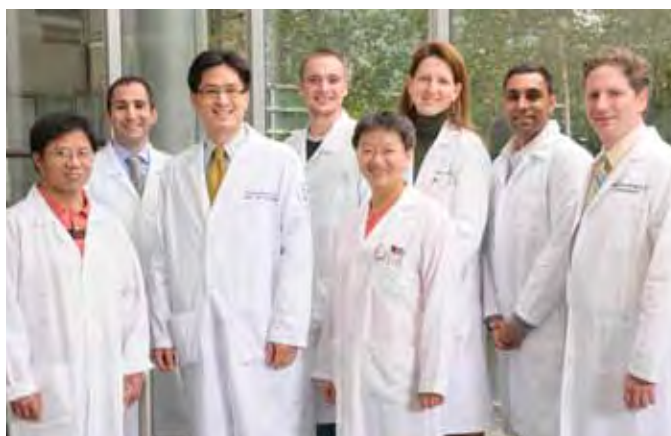
Top: T. Ozawa, PhD, M. Squatrito, PhD, E. Bazzoli, MD  
Bottom: B. Oldrini, PhD, R. Bindra, MD, PhD, L. Barrett, PhD

2009



J. Huse, MD, PhD, L. Barrett, PhD, I. Mellinohoff, MD, O. Becher, MD, T. Ozawa, PhD, T. Pulvirenti, PhD, P. Raju, MD, PhD, A. Lassman, MD, T. Chan, MD, PhD

2008



X. Wang, PhD, O. Becher, MD, R. Young, MD, S. Foster, PhD, R. Huang, PhD, K. Beal, MD, B. Bhatia, PhD, C. Brennan, MD

2007



A. Lassman, MD, L. Cartegni, PhD, A. Hormigo, MD, PhD, M. Bradbury, MD, PhD, M. McDevitt, PhD, D. Ciznadija, PhD

## Faculty Retreats



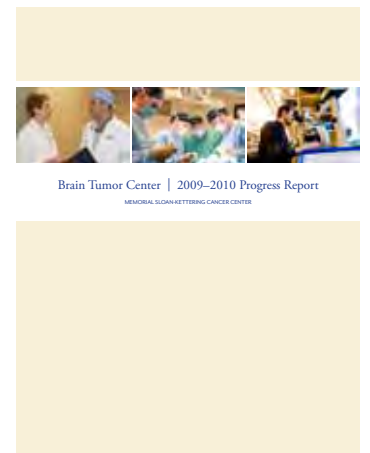
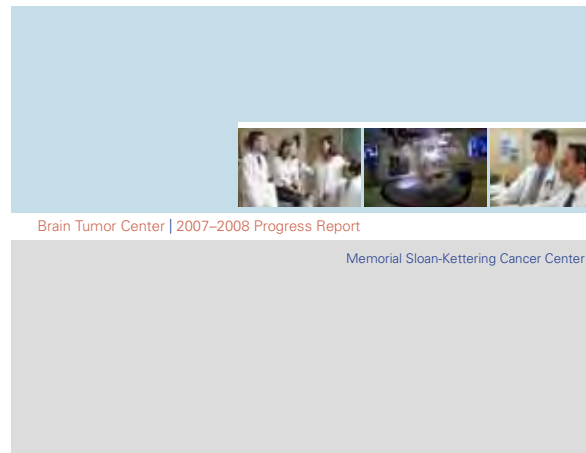
## Medical Student Research Internships



## Shared Equipment



## Progress Reports



## Patient and Caregiver Conference



## Educational Seminar Series (Select Speakers)



Dr. Rosenfeld



Dr. Stiles



Dr. Batchelor



Dr. Parsons



Dr. Aldape



Dr. Heimberger



Dr. Chakravarti



Dr. Cichowski



Dr. Fischbach-Teschl



Dr. Riggins

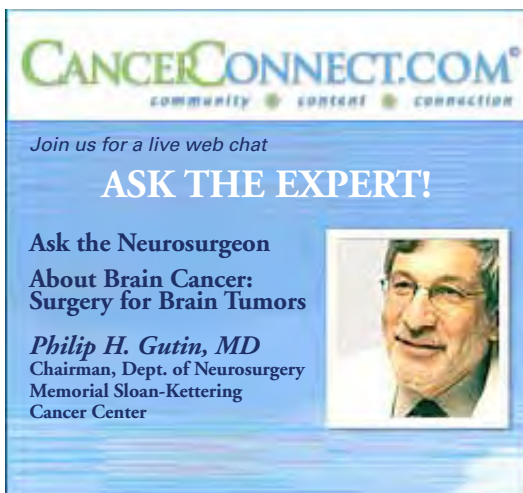


Dr. Iavarone



Dr. Gutmann

## Social Media: Patient and Provider Outreach



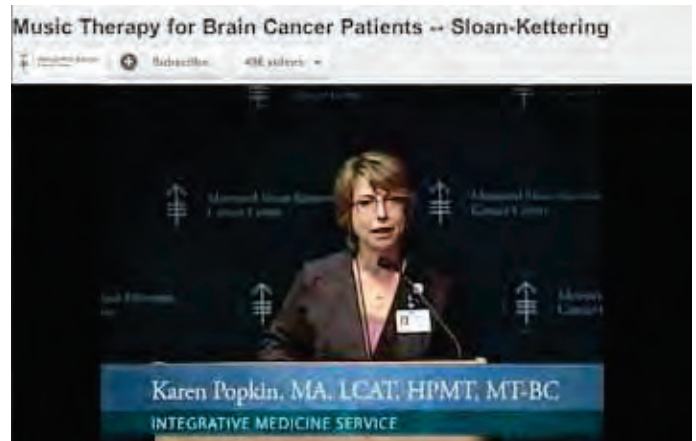
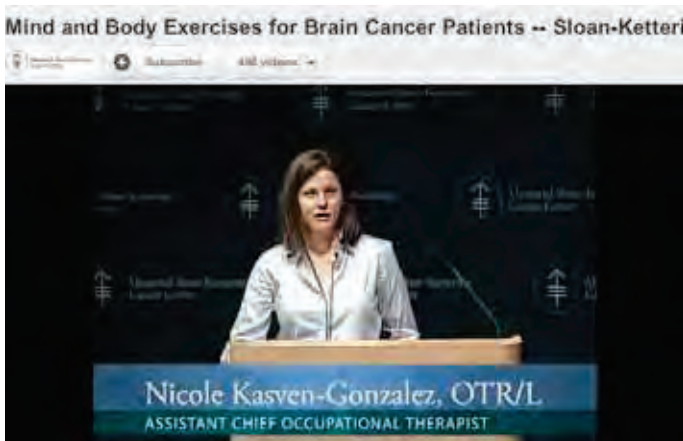
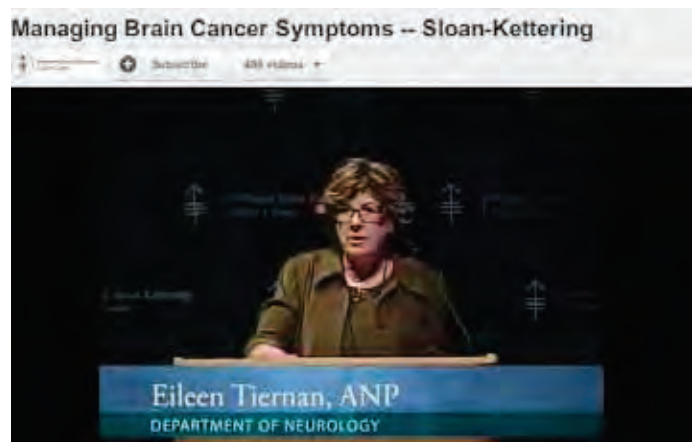
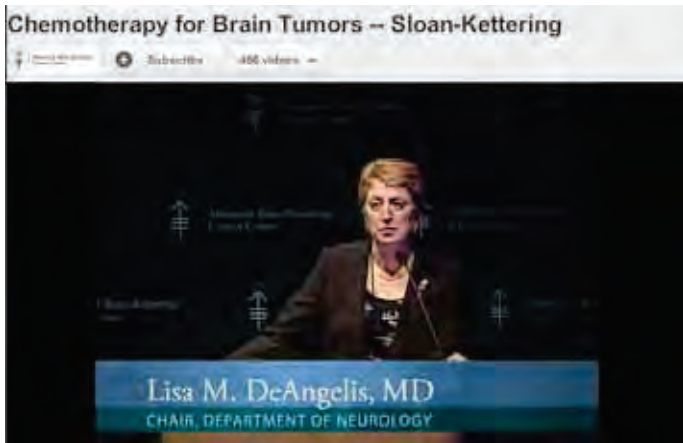
Dr. Gutin participated in a live web chat on July 27, 2011, through cancerconnect.com.



Dr. Bilsky discusses how stereotactic radiosurgery has dramatically improved outcomes for patients with spine tumors.



MSKCC has a YouTube channel dedicated to educational videos for patients, families, and providers. Twelve videos from the educational patient conference are posted and available for viewing at: <http://www.youtube.com/user/mskcc>.



## Eric Holland, MD, PhD

*Eric Holland, Director of the Brain Tumor Center, is both a neurosurgeon and a laboratory investigator. In his laboratory he studies the molecular changes that occur in glioblastoma, the most common and aggressive type of brain cancer, as well as other brain tumors. His research is focused on developing mouse models of brain cancer that mimic the behavior of the disease in patients. While working as a postdoctoral fellow at the National Institutes of Health, Dr. Holland participated in the development of a gene transfer technique known as RCAS/TVA, which uses a bird virus to deliver tumor genes into specific cells in mice. This technique is now used extensively to study not only brain tumors, but a range of different types of cancer. Dr. Holland joined Memorial Sloan-Kettering in 2000.*

### What was the state of glioblastoma research when you first entered the field?

The standard treatment had not changed for decades. It was surgery, followed by radiation and chemotherapy, and it was not very effective for most patients. But in the 1990s, there began to be a lot of analysis of these tumors to try to identify mutations found in them and to try to categorize the tumors by mutational status. Still, not a lot was known up until about ten years ago.

### What has changed in the past ten years?

A lot has happened. One thing is that we've begun to determine which of the mutations we had earlier found in these tumors can actually cause the disease, and which of them simply characterize it. Much of this work was done in my lab, using mouse models to study the result of different genetic changes.

Another finding, which is the subject of ongoing debate, is the concept that not all the cells in these tumors behave the same way, and that some of them are more like stem cells. Stem-like cells are more resistant to therapy, which would help explain why these tumors are so hard to treat.

Arguably the biggest series of events in the past decade has been the categorization of these tumors by molecular criteria, which allowed us to realize that glioblastoma is not one disease, but actually several diseases. Having information about the gene expression and mutational profiles of these tumors allows us to categorize them into groups that have similar biology.



“[We] put glioblastoma tumors into functional groups based on specific genetic changes...[which] would allow us to give patients a more detailed diagnosis in the future... [this has] implications for predicting survival, [and] would allow us to find the best clinical trials for them based on which drug they are more likely to respond to.”

### Do you think the treatment of brain tumors will evolve to the point where patients get different therapies depending on the genetic profiles of their tumors?

The best historical parallel to this is leukemia. At one point, all leukemias were treated as the same disease. All patients got the same treatment, and no one responded very well. Then researchers realized that there were actually multiple different diseases and that they responded to different therapies. Real success in certain subsets of leukemia has come from being able to give someone the most correct diagnosis.

There are many centers around the country, including the Brain Tumor Center here at Sloan-Kettering, that are trying to put glioblastoma tumors into functional groups based on specific genetic changes. This would allow us to give patients a more detailed diagnosis and

have implications for predicting survival. It also would allow us to find the best clinical trials for them based on which drug they are more likely to respond to. We're not (No one is) there yet, but [MSKCC] certainly [has] a lot of technology aimed at this effort.

**In addition to running a laboratory, you're also a surgeon. What role does technology play in the operating room?**

The technology that we use, both functional magnetic resonance imaging (MRI) and intraoperative MRI, allows us to be as safe as possible when we are operating, especially in areas of the brain involved in language, movement, or other critical functions. We are able to map out these areas prior to surgery, so that while we're operating we can look at the MRI scans and we know what areas to stay away from.

But for Sloan-Kettering the real issue isn't even having the technology. Our edge is the expertise with which we use it. To have good surgical outcomes, you need the right people with the right experiences and training, both in the operating room and post-operatively. That's what makes our team as strong as it is.

**How does being a surgeon influence your work in the lab?**

For my own patients, it means that – if they have consented – I can make sure that their tumor tissue that's not required for clinical care and diagnosis is used for research and saved in a tumor bank so that others can study it as well. This is true of all surgeries done at Memorial Sloan-Kettering. Surgery, whether an open resection or a needle biopsy, is the gateway to molecular analysis.

Being a neurosurgeon also allows me to know what the big questions are. I know what we're doing clinically right now to treat

patients – what works and what doesn't work as well. I know what questions we would really like answers to. I am able to aim my research efforts toward understanding these clinical problems, which in the long run will have an impact on the care of all patients.

**We've talked mostly about glioblastoma, because that's the type of brain tumor you're focused on. What other types of brain tumors are the focus of laboratory research within the Brain Tumor Center?**

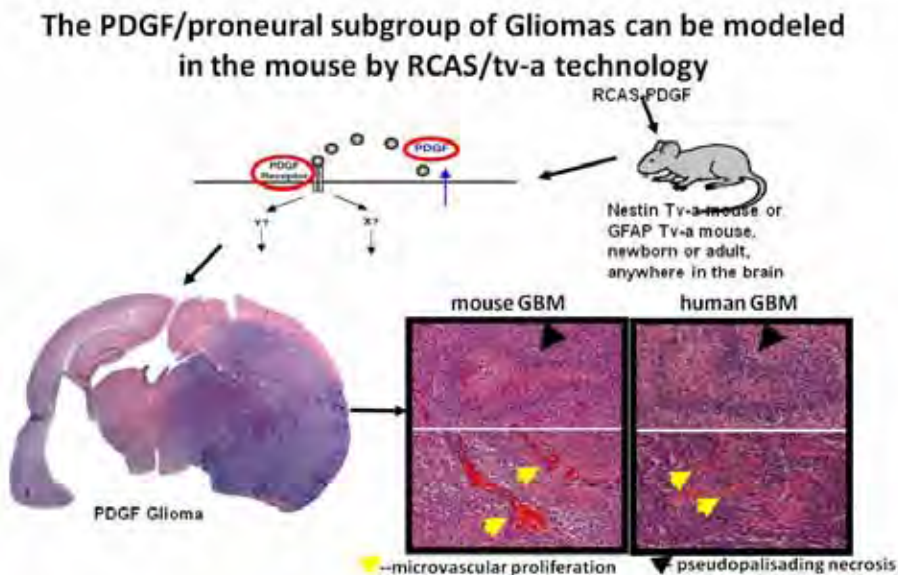
There is a large group interested in studying metastatic disease – cancer that starts in other parts of the body and ends up spreading to the brain. Much of this work is being led by [BTC member] Joan Massagué. The questions that he and others in the BTC are asking is what kinds of genes are expressed in primary tumors that drive the cells to colonize other sites – not just in the brain but other organs as well. As we learn more about the biology, we may find therapeutic targets so that we can attack those cells. We may also be able to use gene signatures to determine which patients are more likely to develop brain metastases.

There's also a fair amount of work going on to understand how these metastatic tumors interact with the brain around them and why they are resistant to standard therapies that are effective against the primary tumor.

**How has the establishment of the Brain Tumor Center enabled the advancement of research?**

The BTC administration helped us write proposals for many of the grants we have received. As a result, BTC members are now participants in several large, multicenter collaborative efforts and consortiums. These include the Mouse Models of Human Cancer Consortium, which promotes modeling of tumors in mice and the technology that is required to do that, and the Tumor Microenvironment Network, which focuses not on tumor cells per se but the environment they live in and how that drives and regulates the formation and growth of tumors. Another one is the Physical Sciences–Oncology Consortium, which has increased collaboration between physical science and biology and the outcome of which has been advances that would not have otherwise happened.

The BTC also has brought together leading experts, people from many areas of Sloan-Kettering who are interested in different aspects of brain tumor research as well as in related areas. Because of the organization of the BTC and its collaborative nature, we're in a position to capitalize on findings that show up in our own labs or the labs of any of our collaborators. And ideally, looking into the future, we'll potentially be able to bring them into clinical utility sooner than almost anyone else.



*Research in the Holland lab focuses on glioma tumor modeling, which can then be treated with tailored drugs to determine responsiveness based on genetic categorizations.*







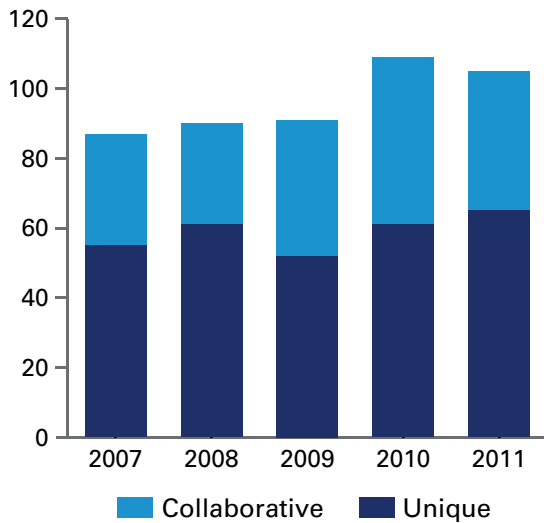
# Metrics

# PUBLICATIONS

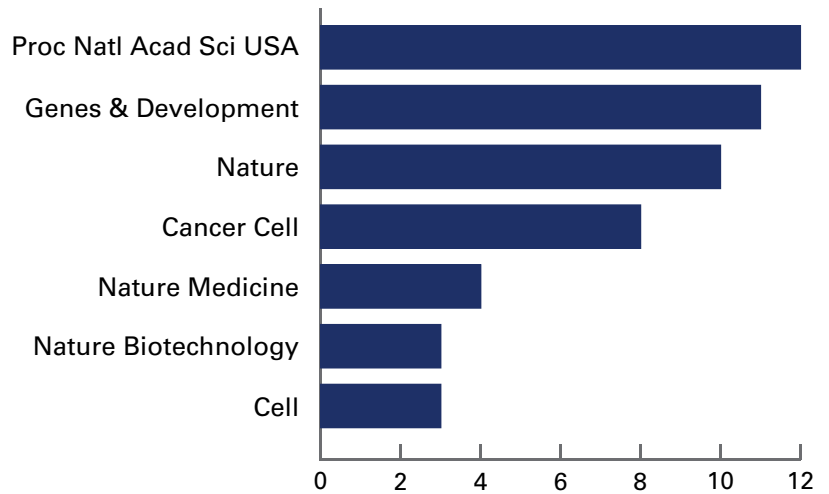
The BTC collects metrics across its members to measure its success. Particular attention is paid not only to the number of publications per year and citations to them, but also to the number of collaborative publications across BTC members. BTC leadership actively promotes interactions that lead to

jointly authored publications. Brain tumor related publications have progressively increased demonstrating the impact of the expansion of the neuro-oncology program at MSKCC and recruitment of dedicated physician-scientists with an interest in brain tumors.

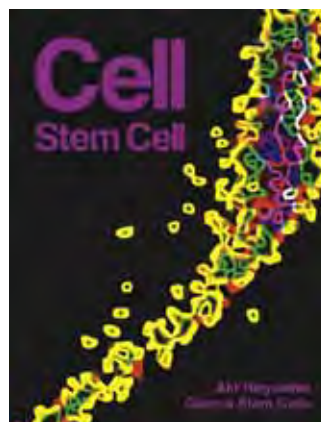
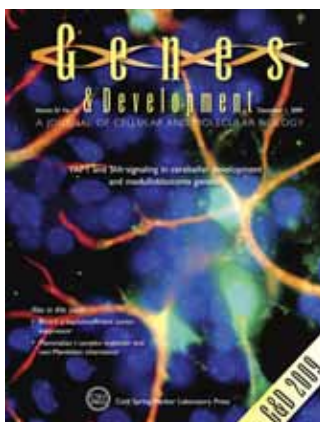
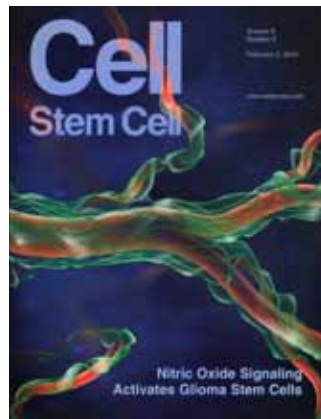
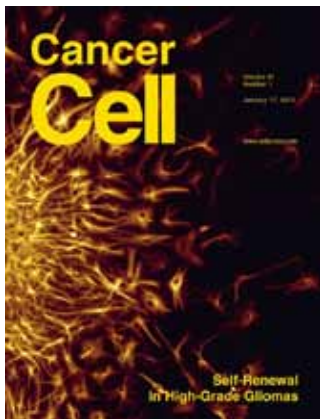
**Total Publications by BTC Faculty, n=482**



**Total Publications in Top Journals (51)**



## Select Journal Covers by BTC Faculty



## NOTEWORTHY

**Patents:** BTC faculty hold over 20 patents related to protein markers, transgenic mice, opioid receptors, polypeptides, signaling pathways, and carcinoma-related genes.

**Startups:** In 2012, a startup company exclusively licensed the C dot silica nanoparticle technology co-developed by Michelle Bradbury, MD, PhD, who, along with Steven Larson, MD, aims to create new targeted multimodal (PET-optical) probes that will both diagnose and treat cancers, while efficiently clearing the body.

### Select BTC Member Accomplishments

#### 2007

Xuejun Jiang	American Cancer Society Scholar
Anna Kenney	Pediatric Brain Tumor Foundation Award
Johanna Joyce	Rita Allen Foundation Faculty Development Award
Joan Massagué	Passano Laureate Prize
Ingo Mellinghoff	Sontag Foundation Distinguished Scientist
Samuel Selesnick	President: New York Clinical Society
Songhai Shi	Whitehall Foundation Award; Dana Foundation Award
Mark Souweidane	Program Chair, American Society of Pediatric Neurosurgery
Robert Young	Norman E. Leeds Award, Eastern Neuroradiological Society

#### 2008

Ronald Blasberg	Paul C. Aebersold Award for Outstanding Achievement in Basic Nuclear Medicine Science, Society of Nuclear Medicine Annual Meeting
Cameron Brennan	Preuss Research Award, Congress of Neurological Surgeons
Andrew Lassman	Preuss Award in Neuro-Oncology, American Academy of Neurology
Ingo Mellinghoff	Doris Duke Clinical Scientist Development Award
Charles Sawyers	Member, Institute of Medicine
Songhai Shi	NARSAD Young Investigator

#### 2009

Lisa DeAngelis	Gary Lichtenstein Humanitarian Award, Voices Against Brain Cancer
Eric Holland	Voynick Award; Member, Institute of Medicine
Hedvig Hricak	President, RSNA; President-elect, International Society for Strategic Studies in Radiology
Jason Huse	Leon Levy Foundation Young Investigator
Alexandra Joyner	President, Society for Developmental Biology; Member, Institute of Medicine
David Lyden	Career Achievement Award, Belgium Society of Cell Biology and Development
Joan Massagué	G.H.A. Clowes Memorial Award, American Association for Cancer Research

#### 2009 (continued)

Ingo Mellinghoff	Advanced Clinical Research Award in Glioma, American Society of Clinical Oncology
Charles Sawyers	Dorothy Landon-AACR Prize for Translational Cancer Research; Lasker-DeBakey Clinical Medical Research Award
Samuel Selesnick	President, American Neurology Society
Mark Souweidane	Nina W. Werblow Charitable Trust Award; President, New York Society for Neurosurgery

#### 2010

Cameron Brennan	Leon Levy Young Investigator Award
Timothy Chan	Doris Duke Clinical Scientist Development Award; Sontag Distinguished Scientist Award
Eric Holland	Altman Award
Joan Massagué	Queen Sofia Institute Gold Medal
Antonio Omuro	Preuss Award, American Academy of Neurology
Chris Sander	Co-Chair, Integrative Cancer Biology Program, National Cancer Institute
Charles Sawyers	Member, National Academy of Sciences
Songhai Shi	Blavatnik Award for Young Scientists, New York Academy of Sciences
Viviane Tabar	Preuss Award, American Association of Neurological Surgeons

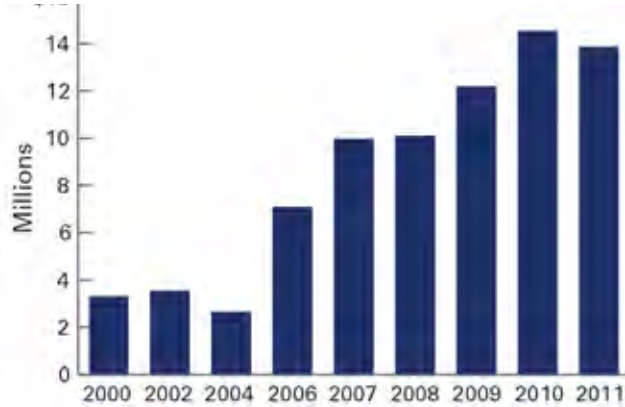
#### 2011

Philip Gutin	President, Neurosurgical Society of America
Andrei Holodny	Norman E. Leeds Award, Eastern Neuroradiological Society
Moritz Kircher	RSNA Scholar Grant
Joan Massagué	Hope Funds Award of Excellence for Cancer Research
Antonio Omuro	Cancer Clinical Investigator Team Leadership Award, National Cancer Institute
Elena Pentsova	Merit Award, American Society of Clinical Oncology
Jerome Posner	Lifetime Achievement Award, Society for Neuro-Oncology
Craig Thompson	American College of Physicians Award
Robert Young	Stephen A. Kieffer Award, Eastern Neuroradiological Society

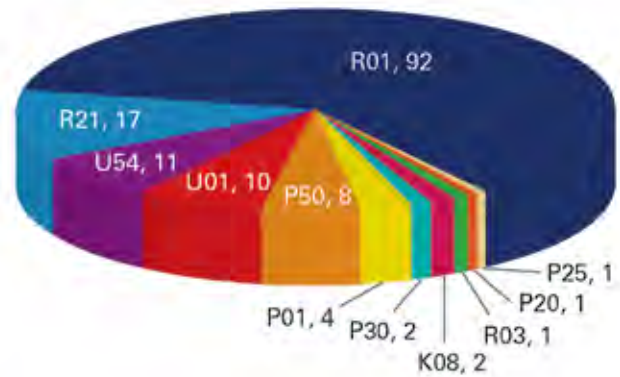
# NIH FUNDING

## NIH Brain-Related Grants, 2000–2011

**Awarded by Year (n=\$77.2M)**



**Total # of Select Grants, by Type**



## Recent Brain-Related NIH Awards

### 2010



**Chris Sander, PI**  
NATIONAL CANCER INSTITUTE  
U54: Systems Biology of Diversity in Cancer



**Songhai Shi, PI**  
NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE  
R21: Clonal Analysis of Neocortical Interneuron Circuit Development



**Gavril Pasternak, PI**  
NATIONAL INSTITUTE on DRUG ABUSE  
R01: Pharmacology of Opioid Receptor Subtypes

### 2011



**Eric Holland, PI**  
NATIONAL CANCER INSTITUTE  
U54: Role of the Perivascular Microenvironment in Primary & Metastatic Brain Tumors



**Timothy Chan, PI**  
NATIONAL CANCER INSTITUTE  
R01: Lucidating the Function of the Widely In-activated Phosfatase PTPRD in the Molecular Patho-genesis of Glioblastoma

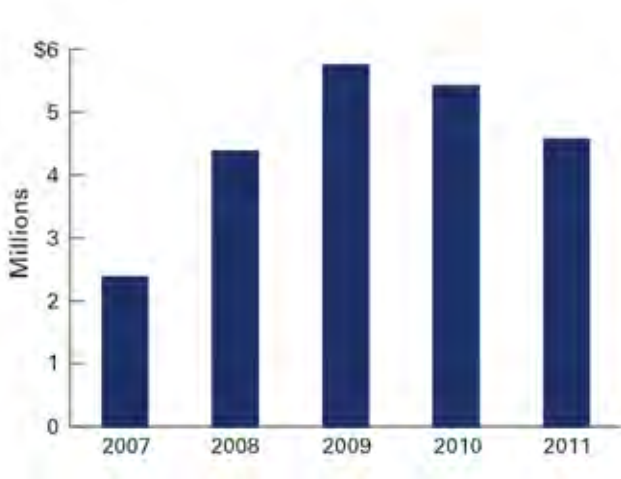


**Robert Benezra, PI**  
NATIONAL CANCER INSTITUTE  
R21: The role of endothelial progenitor cells in tumor growth and metastasis

## BTC FUNDING

### Non-NIH Brain-Related Awards, 2007–2011

Awarded by Year



Awarded by Type



### Major Benefactors of the Brain Tumor Center and Faculty

#### 2007– March 2012

##### \$10,000,000

Simons Foundation

##### \$2,500,000 to \$9,999,999

F.M. Kirby Foundation  
Charlotte and Bill Ford  
Bruce C. Ratner  
Tow Foundation

##### \$1,000,000 to \$2,499,999

Abrams Trust  
Kids for Survival/Schneider Family  
Robert J. Kleberg, Jr., and Helen C. Kleberg  
Foundation  
Leon Levy Foundation  
John and Michael Chandris

##### \$100,000- \$999,999

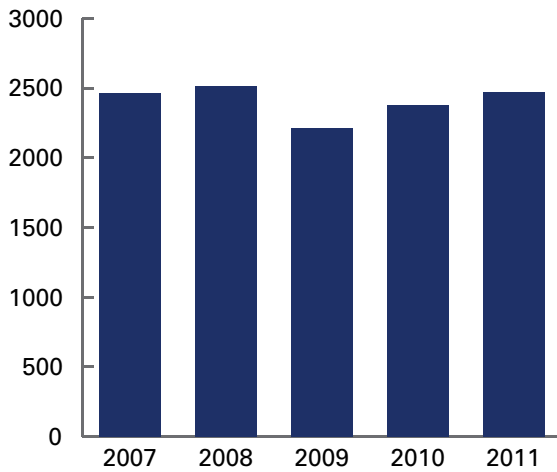
Alex's Lemonade Stand Foundation  
American Brain Tumor Association  
B\*Cured  
Brain Tumor Funders' Collaborative  
Norman Brownstein  
Child Neurology Foundation  
Children's Brain Tumor Foundation  
The Childhood Brain Tumor Foundation  
Dana Foundation  
Genentech  
Daniel S. Goldman  
Sidney Kimmel Foundation for Cancer Research  
The Esther A. & Joseph Klingenstein Fund  
The Gwen L. Kosinski Foundation  
Matthew Larson Pediatric Brain Tumor Foundation  
March of Dimes  
James S. McDonnell Foundation  
McKnight Endowment Fund for Neuroscience  
National Brain Tumor Society  
Silvia Schnur  
Estate of Woodrow Q. Smith  
Sontag Foundation  
St. Baldrick's Foundation  
Voices Against Brain Cancer  
Whitehall Foundation, Inc  
Kendrick R. Wilson III

## ADULT AND PEDIATRIC CLINICAL TRIALS

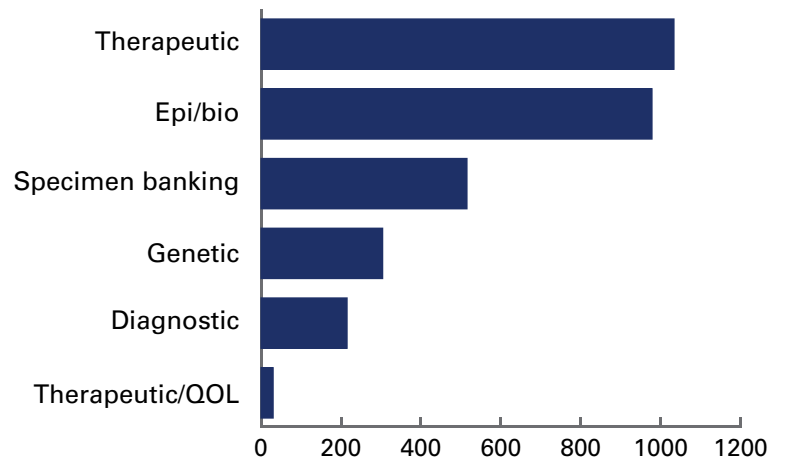
Brain-related clinical trials at MSKCC offer access to new, experimental treatment for patients who have not responded to standard treatments. Our open trials are consistently growing and we have experts in the field bringing new therapies from the laboratories to our patients.

### Brain-Specific Clinical Trial Accruals 2007–2011, n=1,989

By Year

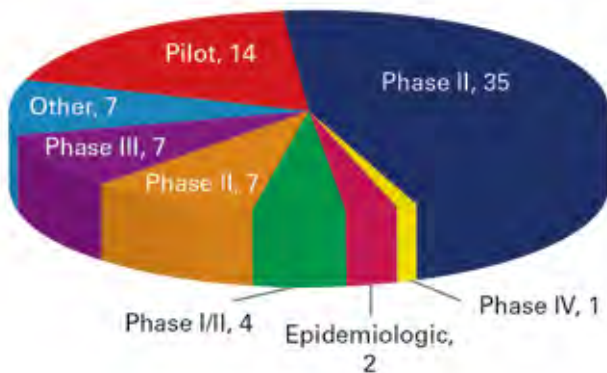


By Type

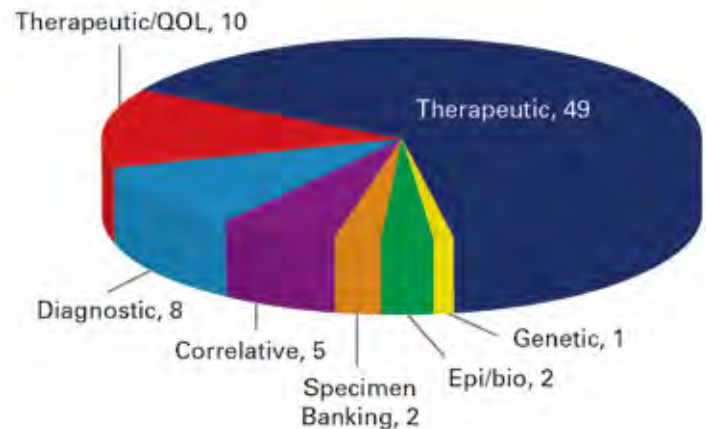


### Open Clinical Trials, 2007–2011, n=77

By Phase



By Type



## Select Open Clinical Trials for Our Patients

### Gliomas

A Phase I Study of RO4929097 in Combination with Standard Radiotherapy and Temozolomide for Newly Diagnosed Malignant Glioma.

**PI: Antonio Omuro, MD**

A Phase I Study of XL765 in Combination with Temozolomide in Patients with Malignant Gliomas.

**PI: Antonio Omuro, MD**

A Phase II Trial of Intensive Chemotherapy & Autotransplantation in Patients with Newly Diagnosed Anaplastic Oligodendroglioma.

**PI: Antonio Omuro, MD**

A Phase III Study of Radiation Therapy with and without Temozolomide for Symptomatic or Progressive Low-Grade Gliomas.

**PI: Thomas Kaley, MD**

Glioma International Case-Control Study.

**PI: Sara Olson, PhD**

Image-Guided Stereotactic Biopsy of High Grade Gliomas.

**PI: Michelle Bradbury, MD**

Phase I/II Trial of Temozolomide and Perifosine for Recurrent or Progressive Malignant Gliomas.

**PI: Thomas Kaely, MD**

Pilot Study of Weekly High-Dose Erlotinib for Recurrent High-Grade Gliomas with the EGFR variant III Mutation.

**PI: Ingo Mellinghoff, MD**

### Brain Metastasis

A Study of [18F]-ML-10 as a PET Imaging Radiotracer for the Early Detection of Response of Brain Metastases of Solid Tumors to Radiation Therapy.

**PI: Kathryn Beal, MD**

### Other

A Phase I Study of LEQ506, an Oral Smoothed Inhibitor, in Patients with Advanced Solid Tumors.

**PI: Alan Ho, MD, PhD**

A Phase II Study of Dose-Dense Temozolomide and Loperamide for Recurrent Low-Grade and Anaplastic Ependymoma.

**PI: Antonio Omuro, MD**

### Pediatric Brain Tumors

A Phase I Study of Convection-Enhanced Delivery of 124I-8H9 for Patients with Non-Progressive Diffuse Pontine Gliomas Previously Treated with Radiation Therapy.

**PI: Mark Souweidane, MD**

A Phase I Study of Intrathecal Radioimmunotherapy Using 131I-8H9 for Central Nervous System/Leptomeningeal Cancers.

**PI: Kim Kramer, MD**

A Phase II Study of Bevacizumab and Loperamide in Children with Recurrent or Refractory Ependymoma.

**PI: Yasmin Khakoo, MD**

A Phase II Study of Intrathecal I131-3F8 in Patients with GD2-Expressing Central Nervous System and Leptomeningeal Neoplasms.

**PI: Kim Kramer, MD**

A Phase II Study of Radiation Therapy, Cetuximab, and Irinotecan in Children and Young Adults with Newly Diagnosed Diffuse Pontine Tumors and High-Grade Astrocytomas.

**PI: Ira Dunkel, MD**

A Phase II Study of Temozolomide plus Irinotecan with or without Bevacizumab in Children with Recurrent or Refractory Medulloblastoma or PNET.

**PI: Kevin De Braganca, MD**

A Phase III Study of Chemotherapy After Radiation in Young Patients with Newly Diagnosed Ependymoma.

**PI: Kevin De Braganca, MD**

Phase I Study of Single Agent Perifosine for Recurrent Pediatric Solid Tumors.

**PI: Ira Dunkel, MD**

Treatment of Atypical Teratoid/Rhabdoid Tumors of the Central Nervous System with Surgery, Intensive Chemotherapy, and 3-D Conformal Radiation.

**PI: Ira Dunkel, MD**

# INTERNATIONAL PRESENCE OF BTC FACULTY

The clinical expertise and innovative research being generated by BTC faculty and leadership is shared across the globe. In the past five years, faculty have been invited to speak on their research findings in 40 US states, 54 countries and across 6 continents.

These engagements consistently maintain the visibility of our research, positioning faculty to cultivate collaborations by providing the opportunity to share information with investigators working with similar techniques, populations, or statistics.



## NORTH AMERICA

### UNITED STATES

#### Alabama

Birmingham

#### Arizona

Carefree  
Phoenix  
Scottsdale  
Tucson

#### California

Anaheim  
Asilomar  
Berkeley  
Coronado  
Huntington Beach  
Irvine  
La Jolla  
Los Angeles  
Orange  
Palm Springs  
Palo Alto  
Redondo Beach  
San Diego  
San Francisco  
Stanford  
Ventura

#### Colorado

Aspen  
Denver  
Keystone  
Snowmass Village  
Vail

#### Connecticut

Hartford  
Middletown  
New Haven  
Stamford  
West Hartford

#### Delaware

Wilmington

#### Florida

Fort Lauderdale  
Hollywood  
Lake Buena Vista  
Miami

Miami Beach  
Orlando  
Palm Beach Gardens  
Palm Coast  
Sarasota  
Tampa

#### Georgia

Atlanta  
Greensboro  
Pine Mountain  
Sea Island

#### Hawaii

Honolulu  
Kohala Coast  
Lani

#### Idaho

Maui

#### Illinois

Waikoloa  
Chicago  
Evanston  
Indianapolis

#### Iowa

Iowa City

#### Kansas

Kansas City  
Lawrence

#### Louisiana

New Orleans

#### Maine

Bar Harbor

#### Maryland

Annapolis  
Baltimore  
Bethesda  
Frederick

#### Massachusetts

Amherst  
Andover  
Boston  
Cambridge  
Cape Cod  
Charlestown  
Chatham  
Framingham  
Provincetown



Waltham  
Worcester

**Michigan**  
Ann Arbor  
St. Joseph

**Minnesota**  
Minneapolis

**Missouri**  
Kansas City  
St. Louis

**Montana**  
Big Sky

**Nebraska**  
Omaha

**Nevada**  
Las Vegas

**New Jersey**  
Bridgewater  
Hackensack  
Jersey City  
Livingston  
Madison  
New Brunswick  
Newark  
Nutley  
Parsippany  
Princeton  
West Orange

**New Mexico**  
Albuquerque  
Santa Fe  
Taos

**New York**  
Buffalo  
Cold Spring Harbor  
East Setauket  
Farmingdale  
Ithaca  
Mineola  
New York  
Old Brookville  
Rochester  
Stony Brook

White Plains  
Williston Park

**North Carolina**  
Chapel Hill

#### Ohio

Cincinnati  
Columbus

#### Oregon

Portland

#### Pennsylvania

Allentown  
Erie  
Farmington  
Hershey  
Philadelphia  
Pittsburgh  
Reading  
Scranton  
Skytop  
South Canaan

#### Rhode Island

Newport

#### South Carolina

Hilton Head

#### South Dakota

Rapid City

#### Tennessee

Memphis  
Nashville

#### Texas

Austin  
Dallas  
Fort Worth  
Galveston  
Houston  
San Antonio  
Smithville

#### Utah

Salt Lake City  
Snowbird

#### Vermont

Burlington

Saxtons River  
Stowe

#### Virginia

Ashburn  
Charlottesville  
Fairfax  
Lansdowne

#### Washington

Seattle

#### Wisconsin

Madison

#### CANADA

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Quebec City  
Toronto  
Vancouver  
Whistler

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Salzburg  
Vienna

### BELARUS

Zhitkovichi

### BELGIUM

Brussels

### FINLAND

Leuven

### FRANCE

Lille

### CROATIA

Dubrovnik

### CZECH REPUBLIC

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### FINLAND

Turku

### FRANCE

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Mandelieu

Paris

St-Jean-Cap-Ferrat

Saint-Raphaël

Versailles





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Heidelberg  
Homburg  
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Travemünde  
Tubingen

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Lausanne  
St. Moritz  
Zurich

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Nagoya  
Osaka  
Tokyo  
Utsunomiya  
Yokohama

**JORDAN**

Petra

**MALAYSIA**

Kuala Lumpur

**RUSSIA**

Sochi

**SINGAPORE**

**SOUTH KOREA**

**TURKEY**

Antalya  
Istanbul

**SOUTH AMERICA**

**ANTIGUA**

**ARGENTINA**

Buenos Aires

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Curitiba  
Porto Alegre  
Rio de Janeiro  
São Paulo

**COLUMBIA**

Barranquilla  
Cartagena

**MEXICO**

**PUERTO RICO**

Cancun  
Mexico City  
Isla Verde

**AUSTRALIA**

Brisbane  
Melbourne  
Renmark  
Sydney

**AFRICA**

**EGYPT**

Alexandria  
Cairo





# Progressive Clinical Care

# MULTIDISCIPLINARY TEAM APPROACH

The Brain Tumor Center takes a team approach to treatment, bringing together experts in highly specialized areas of cancer care. Physicians with expertise in **neuropathology, neuroradiology, neurosurgery, neuro-oncology, radiation oncology, neuroradiology,**

**neuropsychology,** and **rehabilitation** work together to diagnose and treat patients who have brain tumors. Members of the team meet weekly to review and discuss each patient's case and treatment plan in both the adult and pediatric population.

## Example of Multidisciplinary Team

### TREATMENT TEAM

Pediatric Medical Oncology/Neuro-oncology



Ira J. Dunkel   Stephen W. Gilheaney   David C. Lyden   Kim Kramer   Suzanne L. Wolden

Pediatric Radiation Oncology



Pediatric Neurology/Neuro-oncology



Kaleb H. Yohay   Yasmin Khakoc   Kevin C. DeRosier

Pediatric Neurosurgery



Jeffrey P. Greenfield   Mark M. Souweidane

### SUPPORTIVE CARE

Psychiatry & Behavioral Sciences



Abraham S. Bartell

Neuropsychology



Jennifer Ford

Child Life



Alyson Silver

Social Work



Juliana Yiu

### RESEARCH SCIENTISTS



### SPECIALIZED CARE

Cardiology



Laurel J. Steiner

Endocrinology/  
Long term Follow-up



Charles Sklar

### DIAGNOSTIC TEAM

Pediatric Neuroradiology



Sofia S. Haque   Eric Lis

Neuropathology



Marc K. Rosenblum   Jason T. Huse

### NURSING TEAM

Pediatric Practitioners and Research Nurses



Cheryl Fischer   Maria Donzelli   Mary Petriccione   Geraldine Wright

## REHABILITATION & PATIENT SUPPORT SERVICES

Psychiatry and rehabilitation are fully integrated into neurology, to address long-term effects of cancer and its treatment, particularly cognitive impairment



### **Sillerman Center for Rehabilitation (646-888-1900)**

Our experienced neuro-rehabilitation therapists perform detailed evaluations of individuals and provide individual interventions including targeted therapeutic exercise, neuromuscular reeducation and balance training, functional and gait training, manual therapy, caregiver training, home exercise programs and more specialized techniques.

### **Brain Tumor Support Meeting: A Gathering for Brain Tumor Survivors A Meeting for Patients and Families (646-888-4740)**

This is a diagnosis-specific meeting that is co-led by social workers and nurses. It is tailored to give people an opportunity to work on adjustment to life after treatment. This may include changes in physical functioning, appearance, and lifestyle; altered self-image; and fatigue, isolation, and concerns about the future. We encourage people to share concerns while gathering medical and rehabilitation information from healthcare staff.



### **Bendheim Integrative Medicine Center (646-888-0800)**

The Bendheim Integrative Medicine Center offers services designed to enhance quality of life and help prevent and manage a broad range of physical and emotional symptoms. We offer touch therapy, mind-body therapy, acupuncture, creative therapy, and nutrition counseling, as well as exercise programs to improve strength and promote relaxation.

### **Counseling Center: Individual, Family, Couples, and Group Counseling (646-888-0100)**

The Counseling Center welcomes all brain cancer patients — whether or not they are receiving care at Memorial Sloan-Kettering. Our counselors are experienced in structuring counseling sessions to meet the specific needs of each person. These counseling sessions are structured as individual, couples, or family sessions, with some group sessions for patients or family members.

## MAKING AN APPOINTMENT

Appointments to see a neurologist or neurosurgeon at the Brain Tumor Center are usually **available within days**.

Because each patient is different, our professionals speak with patients by phone to determine which physician they should see.

### What to Expect

If appropriate, an appointment will be set up at the time of the call.

**Outpatient neurology and neurosurgery** visits take place in the Rockefeller Outpatient Pavilion at 160 East 53rd Street, on Third Avenue, in midtown Manhattan; some outpatient neurosurgery appointments may take place in our alternate neurosurgery suite on the 4th floor of Memorial Hospital at 1275 York Avenue, on the Upper East Side of Manhattan, between East 67th and 68th Streets.

**Pediatric neuro-oncology and pediatric neurosurgery** patients are seen in the Pediatric Day Hospital located on the 9th floor in the Bobst Building at the main Memorial Sloan-Kettering campus located at 1274 York Avenue.

Our faculty typically would like to review medical records, MRI films, and other test results prior to the patient's first appointment.

Our experts in neurology, neurosurgery, radiology, and radiation oncology meet together to discuss each patient's case, and decide on the best treatment recommendation.

Within a day or two, patients will receive a report by phone, followed by a written report.

#### To Make an Appointment

##### Adult Neuro Patients

866-886-9807

##### Pediatric Neuro Patient

212-639-2336

##### Spine Tumor Center

212-639-3935

##### Pituitary Tumor Center

212-639-6506



## Medical Records Review

A records review is a fast and relatively low-cost way to provide the benefits of Memorial Sloan-Kettering's unparalleled expertise in diagnosis and treatment planning, without the necessity of traveling lengthy distances and leaving the care of local physicians. In recommending treatment, we focus solely on the most expert learning about proven brain tumor therapies, considering individual medical and personal circumstances.

### To Arrange a Medical Records Review

**You can contact us at 866-886-9807 to arrange for a review of your medical records.** When you call, we will discuss with you the best path for you to follow to get our opinion on your care.



**Karen D. Schupak, MD**  
 Director of Radiation Oncology,  
 Regional Care Network;  
 Chief, Basking Ridge  
 Radiation Oncology  
 Appointments: 908-542-3100



**Igor T. Gavrilovic, MD**  
 Neuro-oncologist  
 Appointments: 908-542-3000



## See a Memorial Sloan-Kettering Doctor Closer to Home

Patients living in the suburbs of New York City may find it more convenient to see a Memorial Sloan-Kettering doctor at one of our suburban outpatient cancer centers. Neurologic consultations are available at our Basking Ridge, New Jersey, and Commack, Long Island, locations.

At these regional centers, our expert clinicians see patients in local settings, providing the highest standards of comprehensive cancer care, including the most-advanced chemotherapy and radiation treatments. This means that brain tumor patients need to come to the Manhattan campus only for certain therapy, such as surgery.



**Craig P. Nolan, MD**  
 Neuro-oncologist  
 Appointments:  
 631-623-4100



**Daphna Gelblum, MD**  
 Radiation Oncologist  
 Appointments:  
 631-623-4200



**James Lee, MD**  
 Radiation Oncologist  
 Appointments:  
 631-623-4200



**Brain Tumor Center physicians are experts in the treatment of**  
*Primary Brain Tumors*  
*Metastatic Brain Tumors*  
*Spine Tumors*  
*Pituitary Tumors*  
*Acoustic Neuroma*

## TRANSFORMING PATIENT CARE



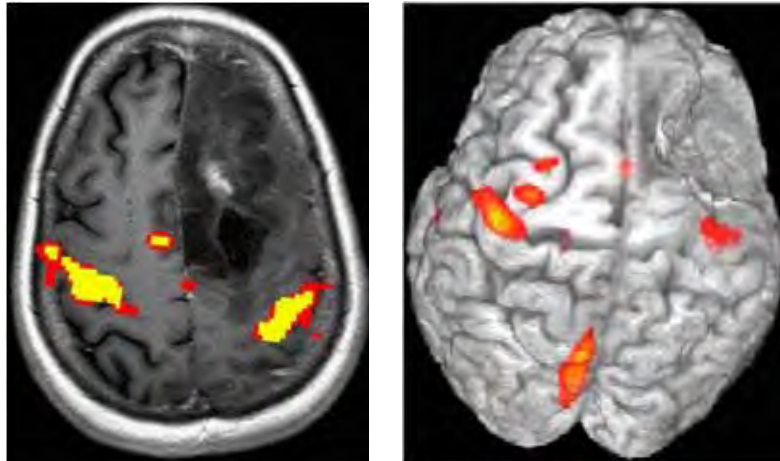
### Intraoperative MRI

Memorial Sloan-Kettering is one of a few hospitals in the country that has an intraoperative imaging suite equipped with a high-field strength magnetic resonance imaging (MRI) scanner in the operating room. Performing brain surgery in this setting allows the neurosurgeon to reevaluate the tumor with MRI during the operation, enhancing precision, **improving the degree of tumor removal, and reducing the need for a second surgery.**

### Innovations in Chemotherapy

At Memorial Sloan-Kettering, our doctors were the **first to use chemotherapy for central nervous system lymphomas and oligodendrogliomas**, and we continue to be at the forefront of developing therapies for these diseases. Our neuro-oncologists are working to develop a number of new chemotherapy drugs, including targeted therapies (drugs that attack cancer cells specifically without harming normal cells), for these and other forms of brain cancer, like glioblastoma.

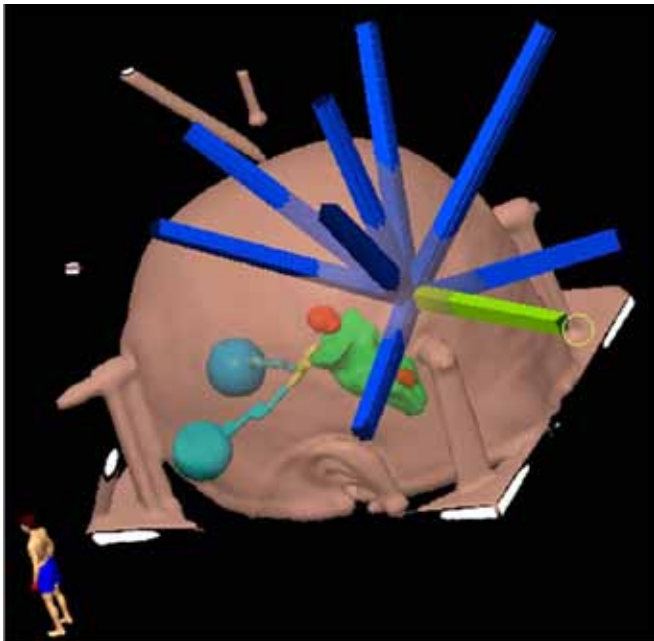




## Functional Imaging & Intraoperative Brain Mapping

Functional magnetic resonance imaging (fMRI) uses high-speed MRI to map areas of the brain associated with vision, speech, touch, movement, and other functions, the locations of which can vary from one person to the next. **The map then allows a surgeon to plan surgery precisely to avoid disrupting these important areas so as to optimize the patient's quality of life.** Many of our brain tumor operations are performed while the patient is awake but sedated. **This kind of sophisticated brain mapping allows the neurosurgeon to remove tumors that are otherwise deemed inoperable, while maximizing preservation of the patient's normal function.**

## BrainLab Technology



Our experts use precise (stereotactic) positioning, computer guidance from MRI scans, and other modern technologies to enable radiation oncologists to deliver these high-dose radiation treatments to tumors anywhere in the brain. Stereotactic navigation, is a computer-aided technology that allows our surgeons to know their position in the brain during surgery. **BrainLab technology was initially tested and used extensively at MSKCC.** This technology is continuously refined and integrated in many aspects of tumor radiation and surgery. Recent data suggest that complete tumor resection can be associated with increased survival in brain tumor patients. At MSKCC, state-of-the-art technology is applied towards this goal. Using intra-operative MRI imaging coupled with stereotactic navigation, our surgeons can obtain information about the extent of tumor resection in real time, while the patient is under anesthesia. This allows them to remove residual tumor during surgery. Operating around eloquent areas of the brain is also made possible by a combination of these technologies with our superlative ability to perform awake intra-operative mapping of the brain. This approach allows our surgeons to maximize tumor resection while protecting areas critical to patient function and quality of life, such as language, movement and memory.

## Antonio Omuro, MD

*Antonio Omuro is a neuro-oncologist who specializes in treating patients with different types of brain tumors. He trained as a doctor in his native Brazil and worked in France before joining the Memorial Sloan-Kettering staff in 2008. Dr. Omuro recently received a Cancer Clinical Investigator Team Leadership Award from the National Cancer Institute — an award that recognizes exceptional clinical investigators for their contributions to the advancement of clinical research through collaborative team science. He is currently the principal investigator for 18 clinical trials at Memorial Hospital, ranging from early-stage trials investigating novel agents to later-stage studies evaluating new ways to use more established drugs and treatments.*

### Could you talk about some recent results from clinical trials that you're particularly excited about?

One idea we're working on is optimizing the use of drugs and other treatments that we already have. A trial we recently finished looked at the daily use of temozolomide [Temodar] for recurrent glioblastoma. The findings were very promising, and now we're looking to see how it compares to other treatments for recurrent disease in glioblastoma patients.

The other trial that we just completed, which was also positive, was testing bevacizumab [Avastin] in combination with a more aggressive radiotherapy schedule. In this study, radiotherapy is given in only six days instead of the 30 treatments people usually receive, but it's more aggressive. In that trial we've had excellent results in patients with unmethylated MGMT, which is the typical patient who does very poorly with this disease. So we're moving forward with a national, randomized phase 2 trial to test that combination against the current standard of care.

### What are some of the trials currently underway that are investigating more novel drugs? Are you looking at any targeted therapies?

Yes, we are looking at several targeted agents and different mechanisms of action. One challenge with drugs that target a particular molecular subtype of brain tumor is that each molecular abnormality is very rare. It's difficult to develop treatments when there is only one patient out of 500 who has a certain mutation. Many patients are treated in the community and have no access to high-end molecular characterization of their tumors and are not even aware that there could be clinical trials tailored for them. We are participating in large collaborative efforts to make those trials feasible. But in the meantime an approach we think is important is



"I do witness how difficult it can be for them [patients], particularly if they develop disabling symptoms, but that is a strong reminder that I need to work harder to develop better treatments for their disease."

to develop treatments that work across the board on more than one subtype of tumor.

One very exciting trial is for a drug called RO4929097. The drug is a gamma-secretase inhibitor, and it targets a pathway called Notch, which is involved in cancer stem cells. There is a theory that there are certain cells within a tumor that behave like stem cells, and that those cells are more resistant to radiation and chemotherapy. The idea of this drug is to transform the cancer stem cells into regular cancer cells to see if they will respond better to radiation and chemotherapy. The trial is for all types of malignant glioma, including glioblastoma, and it's ongoing right now.

We are also participating on a trial targeting macrophages [a type of white blood cell] in what is called the microglia, which is the microenvironment of brain tissue that surrounds tumors. Instead of just trying to address the tumors, we're trying to hit the cells that support and promote tumor growth. It's a completely new concept.

It's being tried for other types of cancer as well, but we think it's most promising for glioblastoma, because glioblastomas depend a lot on the microenvironment of the brain to survive.

In addition, we have trials underway of two drugs that target a pathway called the PI3K pathway. The PI3K pathway is altered in a large number of glioblastoma tumors; up to 60% of patients could potentially benefit.

We are also coordinating with investigators at the Rockefeller University on a dendritic cell [a type of cell in the immune system] vaccine. In this type of treatment, the patients' own dendritic cells are collected and processed in the lab with the patient's own tumor, so that these cells "learn" to recognize the tumor as something to be destroyed. The dendritic cells are then injected back into the patient's blood to produce an immune response against the tumor. This process requires fresh tumor, so the operation has to occur in our center.

#### **What other significant trials are you working on?**

We have several trials in other types of brain tumors as well. One trial that's a bit different is for primary central nervous system (CNS) lymphoma. We're testing whether giving reduced doses of radiation in combination with chemotherapy can improve survival. In primary CNS lymphoma the objective is different from glioblastoma: it's one of the few brain cancers where people can be completely cured, so we want to increase the cure rate in that disease. But we don't want to compromise their quality of life with high doses of radiation because of toxicities.

These patients survive a long time, and over time they can have severe neurological side effects if you use a full dose of radiation. We want to avoid that by decreasing the dose while maintaining the benefit of the treatment. We have completed a phase 2 study on that strategy here, and I'm now leading a larger, national randomized study.

We also have trials for patients with very rare types of tumors such as ependymomas. It is important that these patients also have access to clinical trials, and that their primary physicians refer them to specialized centers for treatment. This is the only way to develop new treatments for these diseases.

#### **What is it like to work with patients who have brain tumors?**

The brain is of course one of the most important and delicate organs in our body. Unlike tumors in other organs, a small growth in the size of a brain tumor can sometimes translate into devastating

symptoms. That makes it challenging for patients and their families to deal with this type of disease.

At the same time, it is very rewarding to take care of these patients. Most patients take the news about their disease really well, and they are strong fighters. In my experience, I rarely have patients who choose not to pursue treatment. They're very keen on the idea of participating in clinical trials and other types of research activities, even when they realize it's more to help future patients than themselves. Their families are very supportive, and I develop very good relationships with them.

I do witness how difficult it can be for them, particularly if they develop disabling symptoms, but that is a strong reminder that I need to work harder to develop better treatments for their disease.

#### **Most patients with brain tumors require several different treatments. How do you coordinate that with other specialists in the Brain Tumor Center?**

Neuro-oncologists work very closely with everyone on the brain tumor team. We refer patients for surgery and radiation when they need it, and we take care of their needs throughout those treatments. We have the brain tumor board that meets weekly to discuss difficult cases where everyone comes together to talk about individual patients and to reach consensus on their treatments. I am very lucky to be surrounded by fantastic colleagues, and we keep learning from each other's experience.



***Dr. Omuro was awarded the 2012 NCI Cancer Clinical Investigator Team Leadership Award for his contributions to the advancement of clinical research through collaborative team science***





# Molecular Neuro-oncology since BTC inception

There has been a major increase in collaborative molecular neuro-oncology research since the inception of the Brain Tumor Center, 2007 to present.

## CENTER FOR CANCER SYSTEMS BIOLOGY (CCSB)

### MSKCC INVESTIGATORS


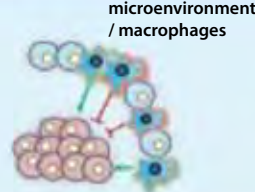
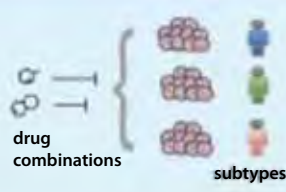
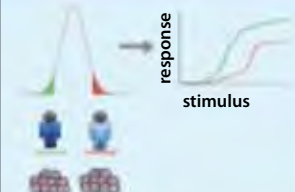
Computational Biology  
**Chris Sander, PhD (PI)**  
**Grégoire Altan-Bonnet, PhD**  
**Christina Leslie, PhD**

The Centers for Cancer Systems Biology funded by the NIH consists of **13 Centers** across the US, focusing on the analysis of cancer as a complex biological system. **A cornerstone of the program is the development and implementation of computational models of processes relevant to cancer prevention, diagnostics and therapeutics.** The integration of experimental biology with mathematical modeling will result in new insights in the biology and new approaches to the management of cancer. **The program brings clinical and basic cancer researchers together with researchers from mathematics, physics, information technology, imaging sciences, and computer science to work on key questions in cancer biology.**

### Overview of the four research subprojects of the CCSB

The research program of the CCSB is divided into **four inter-related subprojects** that integrate novel computational techniques with biological experimentation to investigate tumor cell heterogeneity both within tumors and among patients to gain insight needed for the development of subtype-specific and patient-specific customized therapies.

### Systems Biology of Diversity in Cancer

	Subproject I	Subproject II	Subproject III	Subproject IV
Project Name	Variability of cellular responses to growth factors and drugs during tumorigenesis	The tumor microenvironment in cancer progression and metastasis	Regulatory network differences in diverse tumor subtypes	Endogenous heterogeneity of signaling pathways in cancer
Graphical Summary				
Clinical Application	Targeting the IL-6 pathway: mediator of tumorigenesis and chemoresistance.	Combination therapies that target the tumor microenvironment.	Combination therapies that target clinical subtypes and drug resistance.	Improved clinical markers leading to better differential diagnosis.

## Project 1 (PI: Grégoire Alton-Bonnet):

### Understanding cellular dynamics during oncogenesis and treatment, taking into account the heterogeneous distribution of tumor cells on a uniform genetic background.

Specifically, we are examining the relationship between two dominant signaling pathways driving tumorigenesis, namely the IL-6/Jak/Stat3 and EGFR/RAS/ERK signaling pathways, in two model systems (melanoma and lung cancer) to explore the molecular consequences of inhibiting one or both of these pathways and the resultant phenotypic diversity in monoclonal populations of tumor cells.

## Project 2 (PI: Christina Leslie):

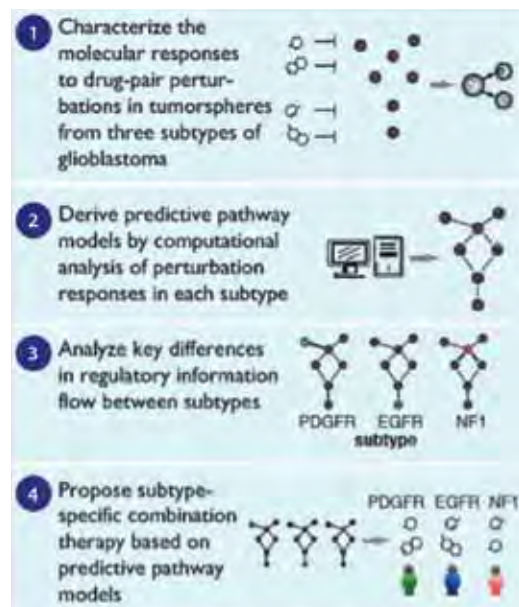
### Dissecting and modeling communication between tumor cells and the host microenvironment to determine how these complex interactions contribute to cancer progression and invasion.

We have devised and are using a novel strategy that enables simultaneous analysis of tumor and stromal genes in metastatic breast tumors from three distinct organ microenvironments: bone, lung and brain. Additionally, we have developed computational models of the interactions between cancer cells and tumor-associated macrophages and are applying these models to address key unresolved mechanistic questions relating to tumor and stromal cell interactions.

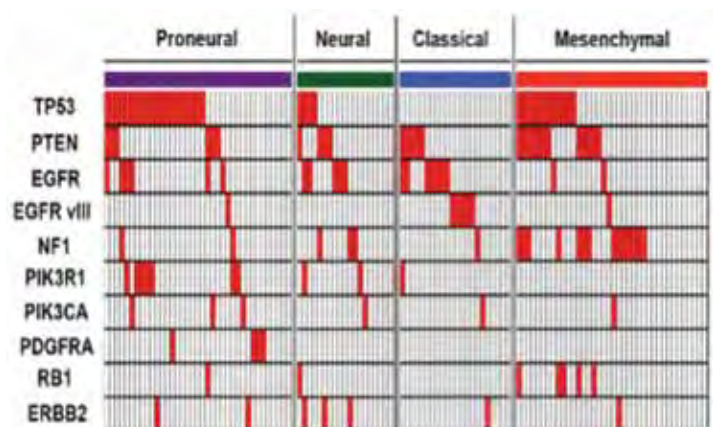
## Project 2 (PI: Chris Sander):

### Investigating differences in regulatory processes leading to patient-patient heterogeneity for a specific cancer, such as differences in regulatory information flow due to alterations in cell signaling networks that establish cancer subtypes, as described above for GBM.

We are also studying differences in expression levels of key signaling regulators that underlie functional heterogeneity in a population of cancer cells. Specifically, we are investigating the molecular mechanisms that underlie chronic lymphocytic leukemia (CLL) and explain the shift of signaling responsiveness in CLL B cells compared to normal B cells.



Systems biology approach to studying drug response in GBM cell lines



Clustering of GBM samples by activation of particular sub-pathways (top, red=alteration by mutation or copy number change). Sources: Cameron Brennan & Nikolaus Schultz

# TUMOR MICROENVIRONMENT NETWORK

The NCI has funded eleven groups to form a Tumor Microenvironment Network (TMEN) to generate a more comprehensive understanding of the composition of the stroma in normal tissues. The goal is to delineate the mechanisms of tumor-stromal interactions in human cancer and to fully understand the role of the tumor microenvironment in cancer initiation, progression and metastases.

## INVESTIGATORS

Cancer Biology and Genetics  
**Eric Holland, MD, PhD**  
**Joan Massagué, PhD**

Pathology  
**Jason Huse, MD, PhD**

Administration  
**Desert Horse-Grant**

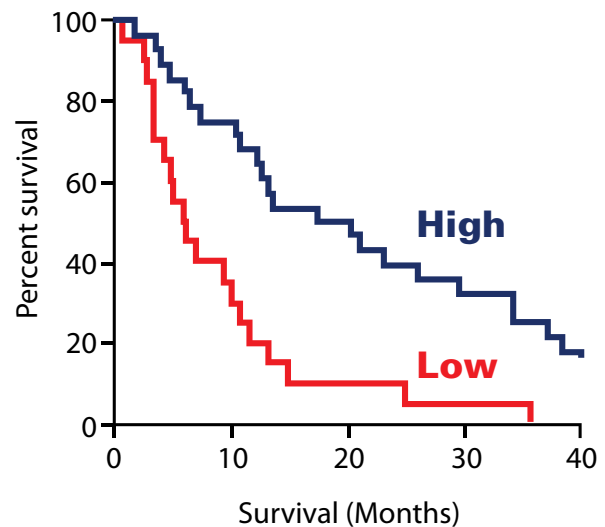
Weill Cornell Medical College  
Medicine  
**Shahin Rafii, MD**

The TMEN at MSKCC investigates the role of vasculature and the stromal cells of the perivascular niche in primary and metastatic brain tumors. The investigators use a combination of engineered mouse models, human surgical samples, and human cell line to investigate the contribution of these cells to tumorigenesis and resistance to therapy.

## Project 1 (PI: Eric Holland):

### The Proneural Perivascular Niche and Therapeutic Response

Glioblastomas (GBMs) are divided into 3-4 molecular subgroups groups, one of which is the PDGF/proneural GBMs that comprise approximately 25-30% of these tumors. The perivascular niche of these PDGF/proneural GBMs is a complex environment. It is composed of multiple cell types, some neoplastic cells derived from the tumor itself and others non-neoplastic cells derived from the stroma. These stromal cells include the endothelia themselves, reactive astrocytes, microglia, smooth muscle cells and fibroblasts. The interplay between these cell types regulates differentiation, tumor progression and response to therapy. Our hypothesis is that endothelial cells, microglia and/or reactive astrocytes express the genes that predict survival in human proneural GBMs and that the expression of some of these genes will affect the response of the tumor cells to radiation and temozolomide.



*Survival of humans with proneural/PDGF GBM when stratified by the expression of 3 genes identified as elevated in recurrent mouse gliomas from trials. Highest half of expression of these genes shows a median survival of 18.5 mos. The lowest half correlates with a survival of 5.8 mos.*

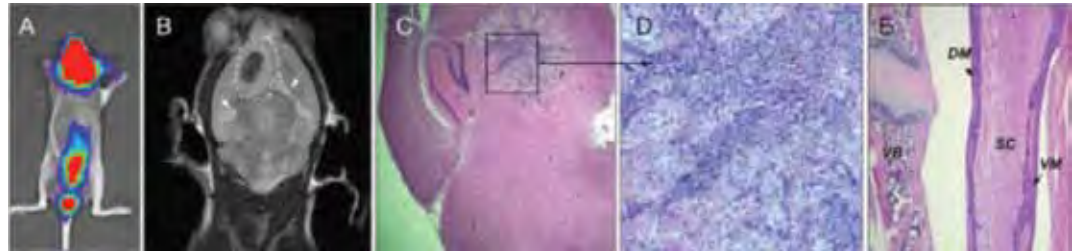


## Project 2 (PI: Joan Massagué):

### Brain Metastasis Microenvironment and Mechanisms

The two main sources of cerebral metastasis are lung adenocarcinoma and breast adenocarcinoma, and as such these two modalities are the principal targets of the study by Massagué in Project 2 of this proposal. This research project investigates (a) genes whose expression in the cancer cells mediates pro-metastatic interactions with the brain vasculature and the surrounding stroma; (b) pathways whose activation in the brain endothelium and brain parenchyma cells defines the reaction to infiltrating cancer cells or whose activation in cancer cells in situ denotes a response to the brain microenvironment; (c) genes whose expression in vascular endothelial cells, astrocytes or microglia denotes a reaction to the

infiltrating cancer cells; (d) the role that these pathways and factors play as pro-metastatic mediators in the perivascular niche; and, (e) how the metastasis microenvironment that has been altered with irradiation supports the viability of residual disease and its eventual regrowth.



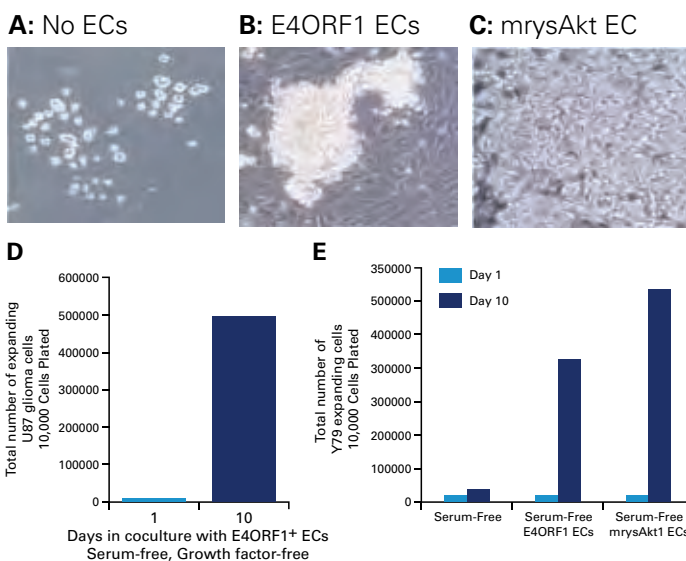
Macroscopic features of our brain metastasis models. A. BLI image of a mouse with brain and leptomeningeal metastasis by CN34-BrM2 cells. B. MRI of brain metastatic lesion (dashed line) showing a hemorrhagic core, and brain edema (arrowheads). C,D. Representative H&E-stained sections of a mouse brain containing a CN34-BrM2 lesion. E. H&E staining of a sections showing MDA231-BrM2a cell colonization of the dorsal (DM) and ventral (VM, meninges; SC, spinal cord; VB, vertebral body). Original magnification, 35.

## Project 3 (PI: Shahin Rafii):

### Endothelial-derived Angiocrine Factors in Progression of Brain Tumors

It is necessary to identify and target key angiocrine factors that are upregulated by brain tumor ECs, in the hope of abrogating brain tumor growth and metastasis as well as reversing resistance to standard therapy. The Rafii lab will take advantage of the brain tumor models established in the

Holland lab (PDGF/proneural GBMs) and metastatic lung and breast xenograft models developed by the Massagué lab to identify the key angiocrine factors induced in the ECs that initiate and sustain brain tumors.



E4ORF1 and Akt-activated ECs support the expansion of neural derived tumors in serum-free and growth factor-free cultures. Human U87 glioma and Y79 retinoblastoma cell lines were co-cultured with serum-free or growth factor-free medium (A) or E4ORF1 (B) or mrysAkt1 activated ECs (C) for 10 days in X-vivo serum-free and growth factor-free conditions. Then the number of expanding U87 glioma cells (D) and Y79 retinoblastoma cells (E) were quantified by flow cytometry (n=3). There was no expansion of the cells in the serum free conditions (A,D,E) while there was significant expansion of the glioma cells in co-culture with either E4ORF1+ ECs (B,D,E) or mrysAkt1 activated ECs, forming large adherent neurosphere-like colonies.

# PHYSICAL SCIENCES–ONCOLOGY CENTER (PSOC)

## Evolutionary Dynamics of Brain, Lung And Hematopoietic Tumor Development

MSKCC, Dana-Farber Cancer Institute, City College of New York, and Vanderbilt University

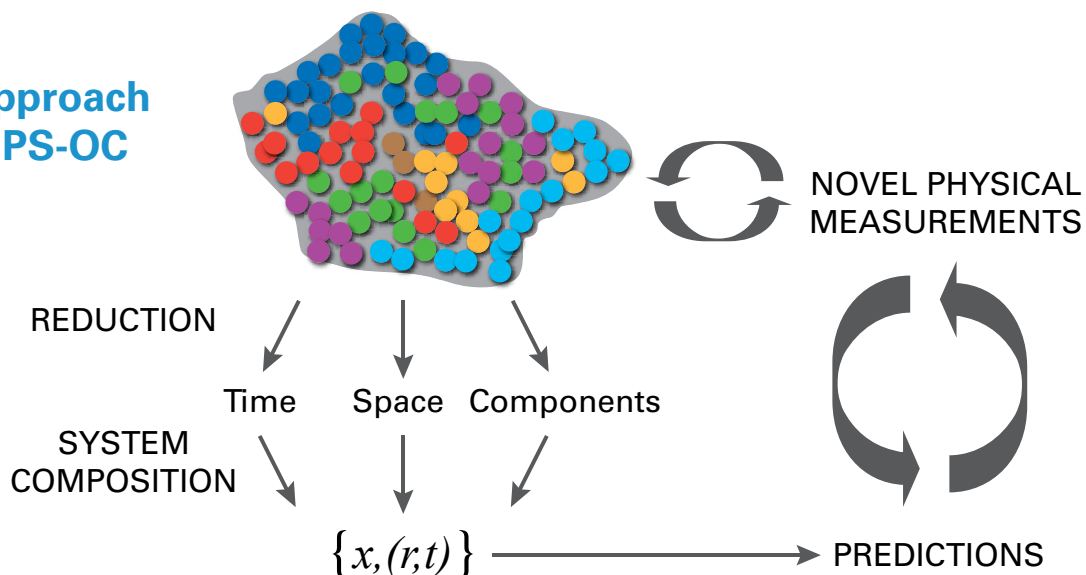
Physical Science Investigators		Cancer Biology & Oncology Investigators
<b>Franziska Michor, PhD:</b> Evolutionary Theory & Mathematics	↔	<b>Eric Holland, MD, PhD:</b> Brain Cancer Biology & Surgery
<b>Rameen Beroukhim, MD, PhD:</b> Cancer Genomics & Bioinformatics	↔	<b>Ross Levine, MD:</b> Leukemia Biology & Oncology
<b>Rong Fan, PhD:</b> Chemistry & Nanoengineering	↔	<b>Ingo Mellinghoff, MD:</b> Brain Cancer Biology & Oncology
<b>Jasmine Foo, PhD:</b> Applied Mathematics	↔	<b>William Pao, MD, PhD:</b> Lung Cancer Biology & Oncology
<b>Kevin Leder, PhD:</b> Applied Mathematics	↔	
<b>Chris Sander, PhD:</b> Physics & Comp Biology	↔	
<b>Maribel Vazquez, PhD:</b> Engineering & Nanotechnology	↔	

The PS-OC advances our understanding of the physical principles that govern cancer initiation, progression, response to treatment, and the emergence of resistance.

1. **Build a mathematical framework** that allows an initial set of experiments to obtain physical measurements of the system, through **investigation of both in vitro and in vivo models**, with emphasis on single-cell measurements to capture the diversity and heterogeneity of the system.
2. These measurements **update the mathematical framework** and help decide between mutually exclusive assumptions of the models.
3. The updated mathematical framework is used to generate the next set of rationally planned experiments, to inform the validity of the mathematical framework, suggest improvements and provide more quantitative estimates of parameters that are used for modifying the next version of the mathematical framework, **which is in turn utilized to propose novel experiments**.

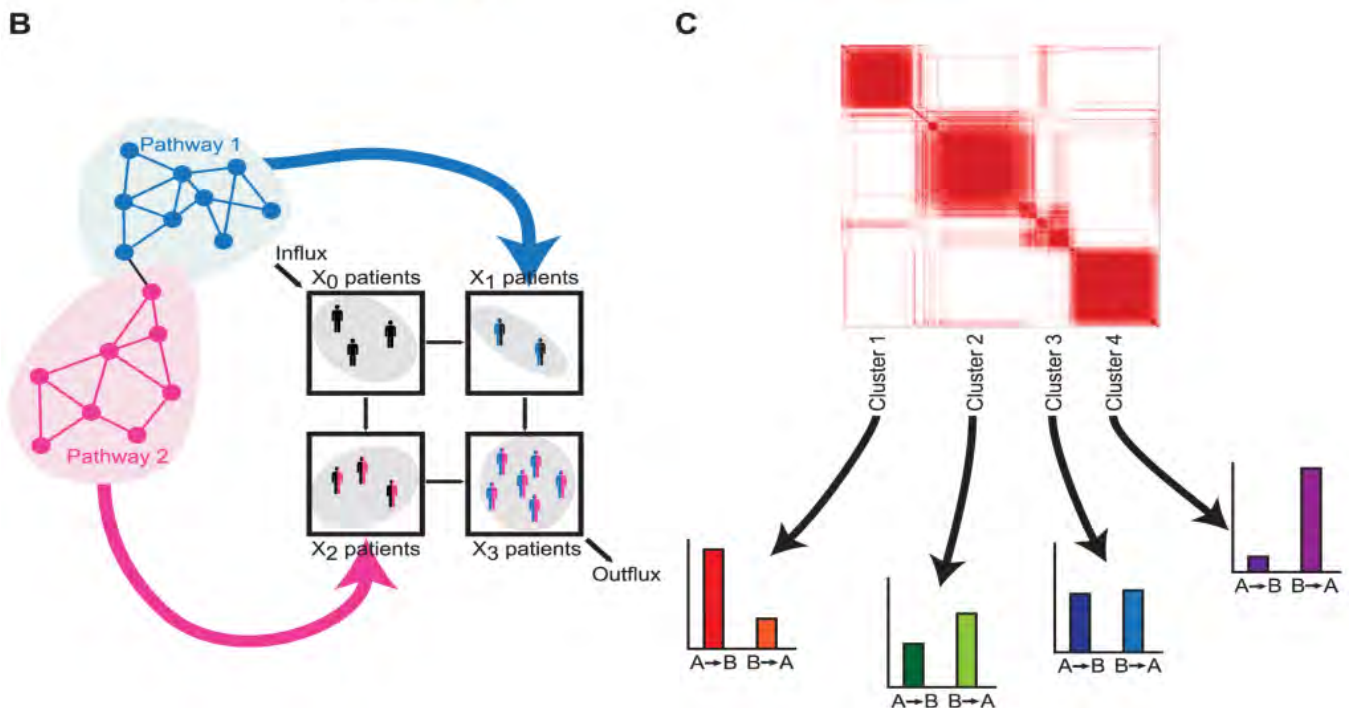
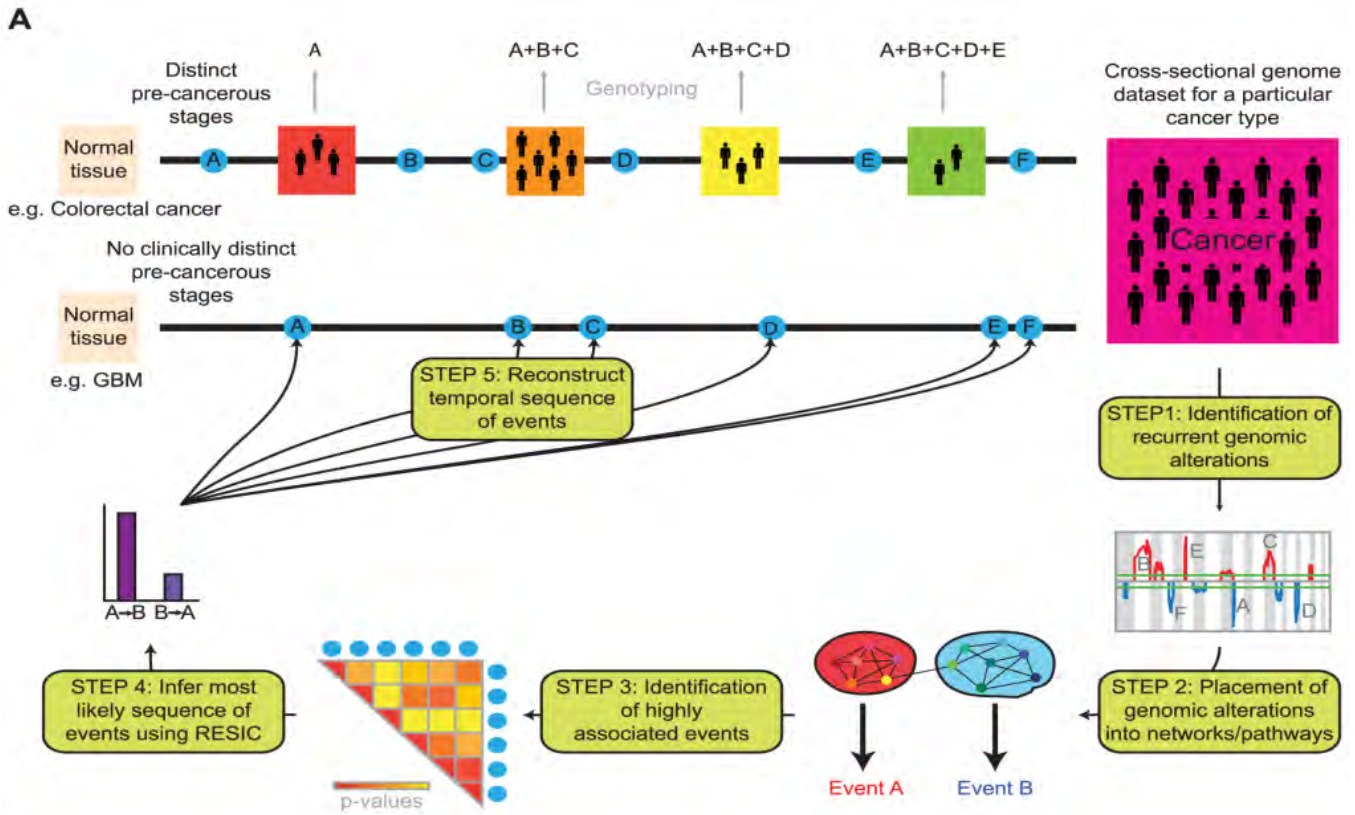


### The Approach of the PS-OC



# A RECENT PUBLICATION

## A Mathematical Methodology for Determining the Temporal Order of Pathway Alterations Arising during Gliomagenesis, Feb 9, 2012, PLoS Computational



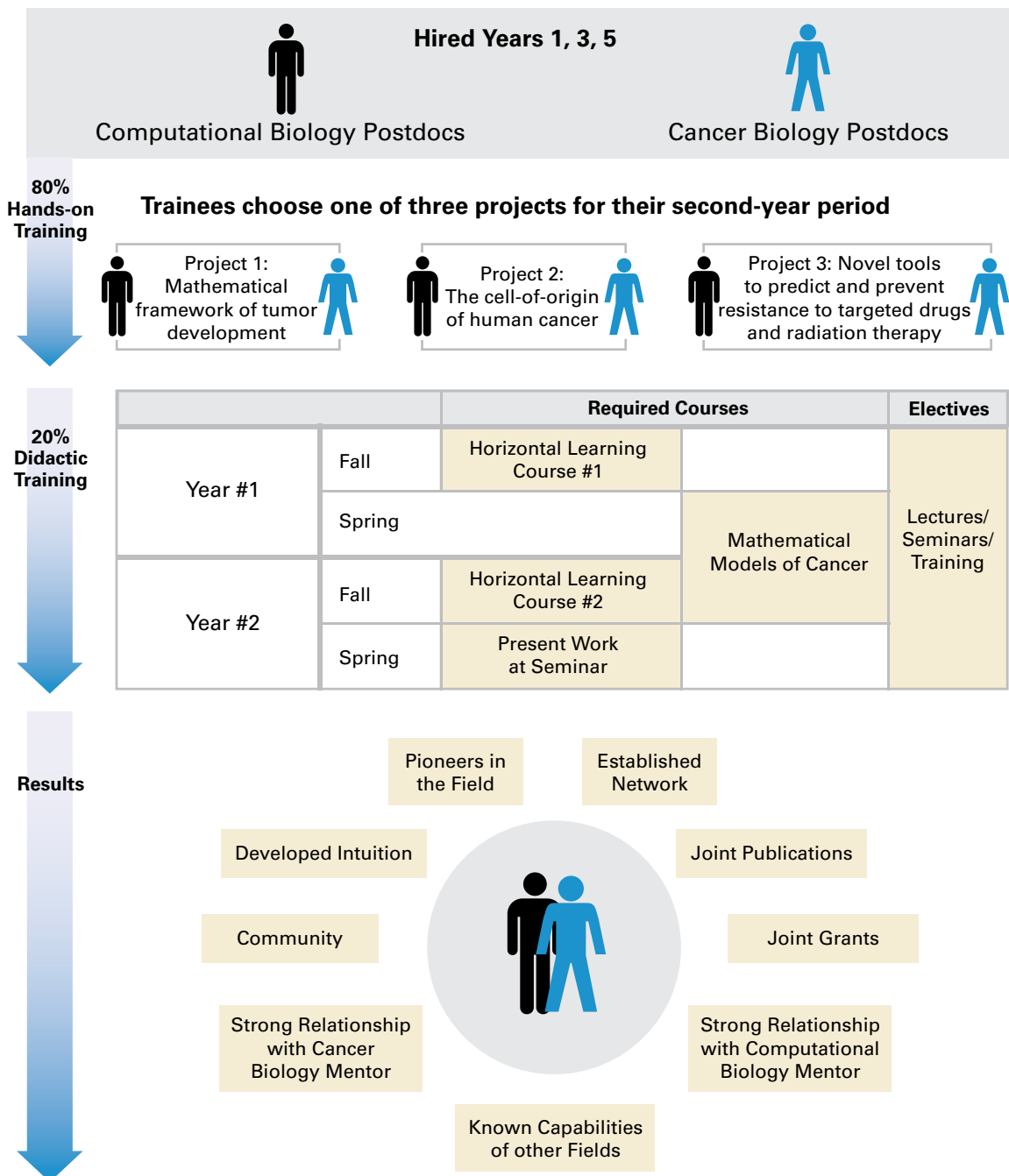
The methodology of pathway-driven RESIC

## PS-OC T32

The Brain Tumor Center was recently awarded a PS-OC Training grant for the purpose of creating a trans-disciplinary training program converging the physical sciences with cancer biology and fostering a new research field. This is the first time MSKCC will have a training program that will train young investigators to be at the interface between cancer biology and computational biology.

The work proposed in this PS-OC Training Program will produce researchers that are trained in both computational and cancer biology to address questions in cancer research with novel, interdisciplinary techniques. Trainees will be embedded into an already existing, highly interconnected physical science oncology network to help answer several key questions in oncology. By establishing a physical science oncology training program, we will drive forward the interdisciplinary study of cancer and establish mathematical modeling of cancer as an independent discipline.

### Physical Sciences-Oncology Center – Training Program



# MOUSE MODELS OF HUMAN CANCER CONSORTIUMS

## U01: P3K Signaling and Biology of Therapeutic Response in Brain and Prostate Tumors

### INVESTIGATORS

Cancer Biology and Genetics  
**Eric Holland, MD, PhD**

HOPP  
**Charles Sawyers**  
**Cameron Brennan, MD**  
**Ingo Mellinghoff, MD**

Urology  
**Brett Carver**

Pathology  
**Jason Huse, MD, PhD**

This grant represents use of GEMMs for understanding cancer biology and using these animals for preclinical testing leading to human trials. It investigates the biology of therapeutic response in solid tumors with particular interest in the PI3K pathway and cells that are resistant to standard of care treatments. It compares and contrasts three tumor types where the PI3K pathway contributes to oncogenesis and therapeutic resistance, namely medulloblastoma, glioma, and prostate cancer. In the first project several drug combinations will be compared to determine optimal strategies for complete blockade of this signaling pathway in these tumors in vivo. The second aim investigates the character of the cells that survive radiation in the case of brain tumors and androgen depletion in the case of prostate cancer and determine what role PI3K might play in their stem-like and resistant properties. Finally, these mouse models will be used to identify gene expression pathways as biomarkers for therapeutic response that could then be taken from the mouse into human trials. The comparison between these tumor types is expected to be cross informative and potentially identify fundamental aspects of solid tumor biology that have therapeutic implications.

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## U01: Using Mouse Models to Probe the Relationship of Oncogenesis to Development

### INVESTIGATORS

Cancer Biology and Genetics  
**Eric Holland, MD, PhD**  
**Hans Guido-Wendel, MD**

Weill Cornell Medical College  
**Yi-Chieh Nancy Du, PhD**

This grant investigates parallels between development and response of tumors to oncogenes and therapies in 3 different tumor types including glioma. In one project, the response of B Cell Lymphoma to therapy and mechanisms of resistance is being investigated as a function of the tumor genotype. In a second project the effect of oncogenic signaling from the polyoma virus middle T antigen (that activates many of the same pathways as seen in GBM) is being investigated in various cells of the pancreas in the development of pancreatic cancer. And the third project investigates the effects of radiation on the various cell types of gliomas. In addition, the mechanisms of resistance to radiation and the cells that survive radiation are being characterized. Our hope is that we will be able to improve the response to radiation for at least some molecular subsets of GBM.

## Moritz Kircher MD, PhD

*Moritz Kircher, who joined the Memorial Sloan-Kettering staff in 2010, is a physician-scientist with formal training in both clinical Radiology and Molecular Imaging research. In the laboratory, his research is focused on the development of innovative nano-sized materials that can be used to study detailed activities of cells. Specifically, he is developing nanoprobes, which are tiny particles of approximately 100 nanometers in size that can help image and treat tumors. Last year, Dr. Kircher was awarded a three-year Brain and Immuno-Imaging Grant by The Dana Foundation to support his research, and was also named Dana Neuroscience Scholar.*

### How did you get interested in the field of imaging?

I realized in Medical School that imaging might be the best way of diagnosing disease. This is because you don't have to try to detect a disease in an indirect way, such as with a lab test or a stethoscope, but you actually look inside the patient. You can see exactly where the disease is and what the extent of it is. Knowing that also allows you to treat in a more focused manner. That's why I went into Radiology.

### What's the difference between traditional imaging and Molecular Imaging?

Molecular Imaging is a new discipline within Radiology. In contrast to the existing imaging techniques that we currently have in the clinic — like CT, ultrasound, and routine MRI — the goal of molecular imaging is to be able to look at individual cells and what is happening within them, noninvasively from outside of the patient. This way you can assess not just gross anatomy and the size of the tumor, but get much more specific information on cellular and subcellular metabolic processes. This allows us to diagnose disease in a more sensitive and precise way.

### What are some ways Molecular Imaging might benefit patients?

As Molecular Imaging techniques enter the clinic, they will allow for more sensitive and earlier disease detection, and also for more individualized treatment. For example, you may have a cancer patient who has a tumor, but there can be many different genetic alterations in the same type of tumor. Patients may respond better to a particular treatment depending on the underlying molecular etiology of their tumors. So if we had an accurate molecular imaging technique that would be a way to determine the molecular subtype of a patient's tumor. Hopefully this would help us eventually avoid surgical biopsies, which are not straightforward to perform in patients with brain tumors. Also, in patients with metastatic disease not every lesion can be biopsied; but often there is a marked heterogeneity among different metastases with regards to their biology and treatment response. This tumor heterogeneity can only be assessed with whole body molecular imaging techniques.



“We envision using a handheld Raman imaging device during surgery so that the neurosurgeon can do complete excisions without harming any normal, crucial neurological structures.”

Molecular Imaging agents could also allow us to see the extent of tumors and to hopefully detect tumors at such an early stage that the tumor can be completely resected and patients can be cured with surgery alone. In later-stage disease, currently it is very hard to find small metastases, such as for example peritoneal implants, and intraoperative molecular imaging techniques will be needed for complete tumor resections.

If we can combine Molecular Imaging with minimally invasive Interventional Radiology techniques, such as cryoablation and radiofrequency ablation, it may help us to avoid major surgeries altogether in the future.

We can also design smart nanoparticles that get activated and can sense specific parameters of the tumor environment. And we are working on theranostic nanoparticles, which can detect and destroy tumor cells simultaneously.

So in summary, detect early and destroy completely.

### Explain the research you're doing in your lab. What are nanoparticles?

In my lab we are developing new multimodal nanoparticles, also called nanoprobes. These are very sophisticated contrast agents

that have multiple capabilities built into them. They can also have targeting ligands on them — which may be peptides or antibodies — that help them seek out the tumors.

Multimodal means you can see the same nanoparticle with different imaging techniques. For example, we are currently working on refining a nanoparticle that can be seen with MRI, Raman imaging, and photoacoustic imaging. The idea is that this particle can be seen before surgery with MRI, which gives a whole body image of the patient and the tumor to allow for correct staging and optimal surgical planning. Then, during surgery, the same nanoprobe can be seen with Raman and photoacoustic imaging technologies. These are both new modalities that currently are being used in experimental clinical settings.

The advantage of Raman imaging is based on the fact that it is possible, by creating a particular nanoparticle structure and dye composition, to enhance the signal originating from those nanoparticles more than a billion fold. This means that Raman imaging can be more sensitive than other techniques, allowing us to detect a very small number of nanoparticles in living organisms. At the same time the Raman signal is unique (a spectral fingerprint), so when you get the signal, you know you are detecting the nanoprobe and nothing else.

Photoacoustic imaging is a mixture of optical imaging and ultrasound. It combines the high sensitivity of optical imaging with the better depth penetration and the 3D-capabilities of ultrasound. Because it can reach several centimeters into the tumor, it can give the surgeon a road map on how to perform the gross resection. Raman imaging can then be used for the fine resection at the tumor margin.

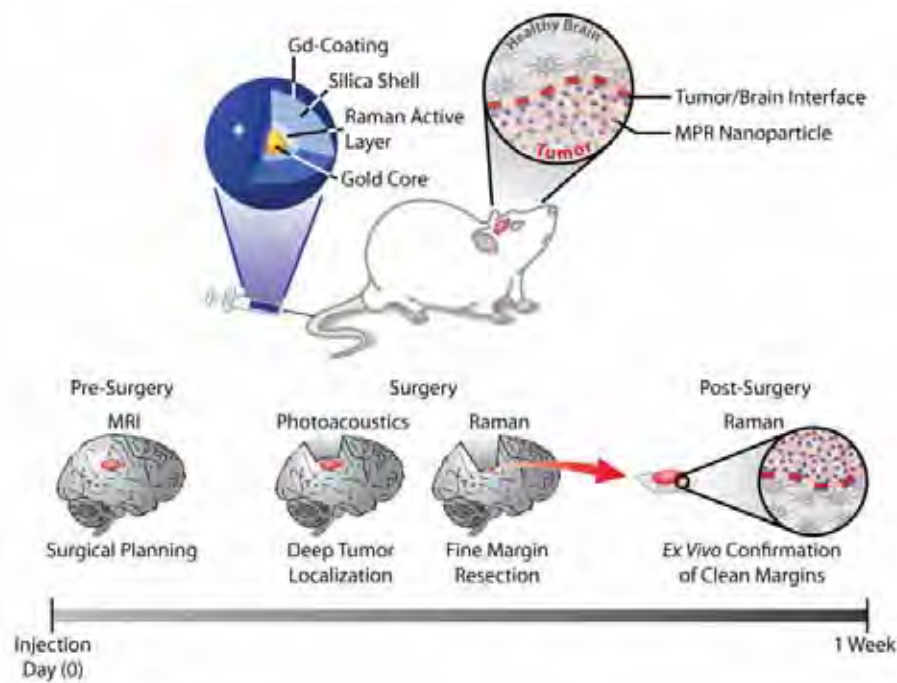
**Does this research have particular applications for the treatment of brain tumors?**

One reason brain tumor surgery is so difficult is that you cannot spare any healthy brain tissue in contrast to other organs such as for example the liver or the lung, where one can remove an entire segment of the organ. As one cannot just perform a “wide excision” of the tumor to get clear margins there are usually small tumor deposits left behind that then cause recurrence. In addition, the margins of brain tumors are often diffuse and infiltrative, with small tumor protrusions extending into the normal brain that cannot be seen with the naked eye. Our nanoparticles have shown to enable visualization of such microscopic tumor tissue in mouse models and we hope this will eventually also work in humans. We envision using a handheld Raman imaging device during surgery so that the neurosurgeon can do complete excisions without harming any normal, crucial neurological structures. Ultimately this principle could be applied to many other areas of the body, but right now we are focusing on the brain to establish a proof-of-principle.

**What needs to be done before this work can move from the laboratory into a clinical setting?**

We have now started to test the nanoparticle imaging method in the most advanced brain tumor mouse models available, which were developed by [Brain Tumor Center Director] Dr. Eric Holland. His models closely resemble human brain tumors, in the way the tumors grow and form very infiltrative margins.

If the technique works well in these models then this is a very good sign it will work in humans. However we will also need to test it in larger animals before human trials. If all the laboratory studies go well and we don't see cytotoxic effects, then we can think about testing it in clinical trials. We think these nanoparticles have a decent chance of being successful because they're based on gold, and that's an inert, nontoxic material that is already used in medical applications.



**Dr. Kircher was awarded a Brain and Immuno-Imaging grant by the Dana Foundation for the development of a dual-modality MRI-Raman nanoparticle allowing combined pre- and intra-operative visualization of glioblastomas.**

*“Novel MRI-Raman-Photoacoustic nanoparticle for combined preoperative and intraoperative brain tumor imaging”, in press in Nature Medicine*

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BTC faculty have authored over 480 publications in the past five years.

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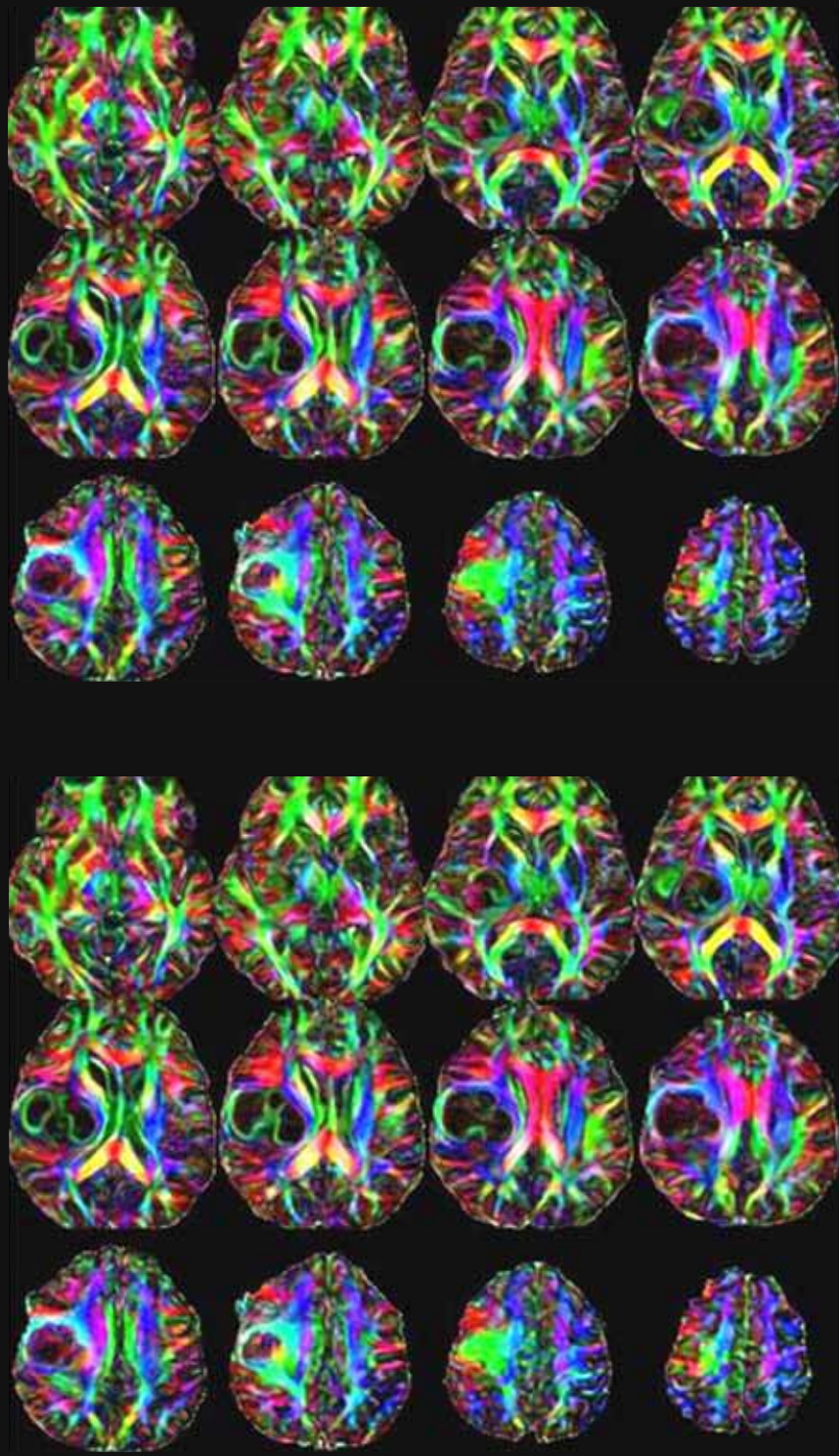
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