3. PROGRAM PLAN

3A. Program Administration

Program Director. The Program Director, **Etty (Tika) Benveniste, Ph.D.**, is the Alma B. Maxwell UAHSF Endowed Chair, Professor and Chairman of the Department of Cell, Developmental and Integrative Biology, and Associate Director, Basic Science Research, Comprehensive Cancer Center, in the UAB School of Medicine. **She will be responsible for the scientific leadership, fiscal matters and administrative execution of the Training Program, spending 10% of her effort on this.** Dr. Benveniste received her Ph.D. in Immunology from UCLA in 1983, and did postdoctoral studies in the field of Neuroimmunology from 1983-1986 at UCLA. Dr. Benveniste was recruited to the University of Alabama at Birmingham as an Assistant Professor in the Department of Neurology in 1986. She was promoted to Associate Professor in the Cell Biology Department in 1992, and then was promoted to Professor in 1995. Dr. Benveniste served as the Director, Graduate Program in Cell Biology, from 1995-2000; as Vice Chair of the Department of Cell Biology from 1997-2000; and then became the Chair of the Cell Biology Department in 2000. Dr. Benveniste also was appointed as the Founding Associate Dean of Postdoctoral Education in 1999, and served in that capacity until 2001. In February 2012, Dr. Benveniste was named as the Founding Chair of the new Department of Cell, Developmental and Integrative Biology, which resulted from combining two basic science departments, Cell Biology and Physiology/Biophysics. Dr. Benveniste has had extensive administrative experience in the training/mentoring of predoctoral and postdoctoral fellows in her capacity as Graduate Program Director of Cell Biology and Associate Dean for Postdoctoral Education. Regarding her individual experience, Dr. Benveniste has mentored over **150** predoctoral fellows, postdoctoral fellows, undergraduates, medical residents, medical students and high school students in her laboratory at UAB since 1988. **In particular, Dr. Benveniste has had thirty-two students receive their Ph.D. from her laboratory, currently serves as Mentor for two graduate students, has trained over thirty postdoctoral fellows, and currently serves as a Mentor to four postdocs**. **The majority of Dr. Benveniste's trainees are in academic research positions.** Dr. Benveniste is a very active teacher at the graduate, medical and postdoctoral levels. In particular, she is heavily involved in the GBS Graduate Program. **She has served on thesis committees of over 120 graduate students** in various departments including Cell Biology, Microbiology, Pathology, Physiology and Biophysics, Neurobiology and Pharmacology.

Dr. Benveniste has been continuously funded as a principal investigator on numerous grants from the NIH, NSF, National Multiple Sclerosis Society (NMSS) and other agencies since 1987. She has presented over 180 invited lectures at national and international meetings, as well as other academic institutions, and has published over **200** original research papers and review articles. Dr. Benveniste has served on numerous NIH study sections since 1988; Special Section for AIDS and Related Research Review Group (Member, 1988-1991); Neurosciences Program Project Review Committee B (Member, 1993-1995; Chairman, 1995-1997); Training Grant and Career Development Review Committee (NST) (Member, 1999-2002); Clinical Neuroimmunology and Brain Tumors (CNBT) (Member, 2000-2004; Chairman 2004-2006); Cellular and Molecular Biology of Glia (Chairman 2007-2010); and is currently a member of the Advisory Board for the NIH Center for Scientific Review (2011-present). She has also served on the American Cancer Society Advisory Committee for Cell Biology from 1993-1995; as a member of the National Multiple Sclerosis Society (NMSS) Grant Review Committee (1998-2003), and as a member of the NMSS Research Programs Advisory Committee (2004-2010). Dr. Benveniste serves on the Scientific Advisory Boards for the SONTAG Brain Tumor Foundation (2003-present), and the Southeastern Brain Tumor Foundation (2005-present). Dr. Benveniste is also a past and active participant on numerous editorial boards, including *Journal of Neuroimmunology*, *Journal of Immunology*, *GLIA, Journal of Neuroscience*, *Journal of Biological Chemistry*, and *Journal of Neurovirology*. Dr. Benveniste was elected as a Fellow of the American Association for the Advancement of Science (AAAS) in 2009, and is President-Elect of the American Society of Neurochemistry (2011-present).

Program Co-Directors. Drs. Steve Carroll and James Markert will serve as the Program Co-Directors of this training grant. Dr. Carroll is responsible for overseeing the Didactic Coursework for pre and postdoctoral trainees, and Dr. Markert is responsible for facilitating the recruitment of resident candidates to this Training grant, and designing their didactic curriculum. **Drs. Carroll and Markert designed the new Brain Tumor Clinical Course. Each will devote 5% effort to the Training Grant.**

Dr. Steve Carroll is a Professor of Pathology, Cell, Developmental and Integrative Biology and Neurobiology and the Director of the Division of Neuropathology. He also serves as the Director of the UAB Brain Resource

Program, Director of the Cellular and Molecular Neuropathology Core Laboratory and Director of the Neuropathology Fellowship Program. He is a Senior Scientist in the Comprehensive Cancer Center and holds appointments as a Scientist in the Alzheimer's Disease Research Center, the Center for Aging, the Intellectual and Developmental Disabilities Research Center, the Civitan International Research Center, the Center for Glial Biology in Medicine, the Center for Neurodegeneration and Experimental Therapeutics and the Comprehensive Neuroscience Center. Dr. Carroll received his Ph.D. in Cell Biology in 1986 and his M.D. degree in 1988 under the auspices of the Baylor College of Medicine Medical Scientist Training Program. He then completed his residency in Anatomic Pathology and his fellowship in Neuropathology at Barnes Hospital and the Washington University School of Medicine (1988-1994). During this time, he also received post-doctoral training in developmental neurobiology in the laboratory of Dr. Jeffrey Milbrandt at Washington University (1990-1993). After completing his clinical training in 1994, Dr. Carroll joined the faculty of the Department of Pathology at Washington University. In 1997, he moved to UAB as an Assistant Professor in the Department of Pathology. He was promoted to Associate Professor in 2001 and became Professor and Director of the Division of Neuropathology in 2008. He has lectured in the Neuropathology course for second year medical students for 18 years and has been very active in the education of pathology, neurosurgery and neurology residents and fellows. Dr. Carroll also lectures in multiple graduate courses within the Neuroscience and Cancer Biology graduate programs and the Howard Hughes Med-to-Grad Program; this includes serving as Co-Director of a very popular weekly Cancer Biology journal club. He has previously served as Co-Director and Director of the UAB Cancer Biology Graduate Program, and is a member of the UAB Medical Scientist Training Program Steering Committee. Dr. Carroll's teaching efforts have been well received by students as indicated by the fact that he has received 18 teaching awards; of particular note, he was named Lecturer of the Year three times at Washington University and at UAB is a two-time recipient of both the President's Award for Excellence in Teaching in the Joint Health Sciences and the Caduceus Club's Donald Taft Memorial Award for Best Basic Science Professor. **Dr. Carroll has directed the doctoral research of 6 graduate students, including 3 M.D.-Ph.D. students, and 8 postdoctoral fellows (7 of whom currently hold faculty positions). He currently serves as the Mentor for two graduate students (one Howard Hughes Med-to-Grad and one M.D.-Ph.D. student).** He has served on the thesis committee of 29 graduate students. In recognition of his commitment to graduate student training, Dr. Carroll received the Graduate School Dean's Award for Excellence in Mentorship in 2011.

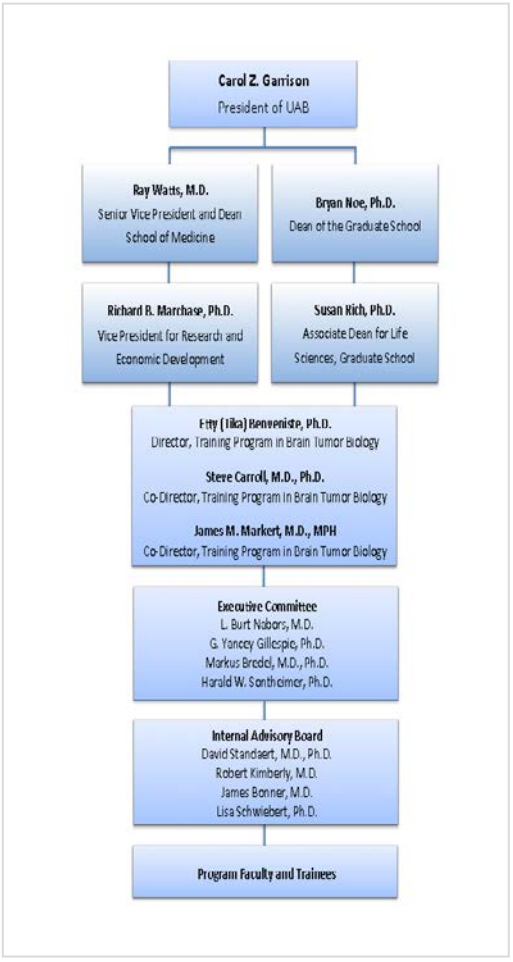
Dr. Carroll has been continuously funded by NIH, the Department of Defense and other agencies since 1996. He has been quite active as an invited lecturer at national and international meetings and at other academic institutions. Dr. Carroll has published over **65** original research papers, invited review articles and book chapters. He served as the Guest Editor on a special edition of Brain Research Bulletin devoted to "Genetically Engineered Mouse Models of Neurologic Diseases". He has served or is currently serving on the editorial boards of *The American Journal of Pathology*, the *Journal of Neuropathology and Experimental Neurology*, *Neuro-Oncology* and *Brain Research Bulletin* and as a reviewer for 45 journals including *Neuron*, *The Journal of Cell Biology*, *Oncogene*, *Cancer Research*, *Nature Reviews Cancer* and *The Journal of Neuroscience*. Dr. Carroll is also the Editor for the Neurobiology of Disease and Development and Repair sections of *Brain Research Bulletin*. Dr. Carroll has served as a member of the National Institutes of Health College of CSR Reviewers and on 25 NIH study sections including Neurogenesis and Cell Fate (NCF), the SPORE in Sarcoma, Brain, Liver, Lung and Prostate Cancers Review Panel, the Drug Discovery for the Nervous System Special Emphasis Panel, the Neurofibromatosis/Tuberous Sclerosis Special Emphasis Panel and the Oncological Sciences Fellowships Special Emphasis Panel. He has also served as a Scientist Reviewer for the DOD on 5 study sections including the Neurofibromatosis-B-Tuberous Sclerosis Complex Review Panel, the TSCRP Tuberous Sclerosis-Basic Science Review Panel and the NFRP Neurofibromatosis-Basic Science Review Panel. Internationally, Dr. Carroll has served as a reviewer for The Wellcome Trust, the National Sciences and Engineering Research Council of Canada, the Association for International Cancer Research, the Italian Ministry for Education University and Research and the Austrian Science Fund.

Dr. James Markert received his M.D. degree from Columbia University College of Physicians and Surgeons along with a *Masters* in Public Health in 1988. He then completed his Neurosurgery residency at the University of Michigan Medical Center. During this time he did postdoctoral training in the laboratory of Dr. Robert Martuza at Massachusetts General Hospital from 1990-1991. After completing his neurosurgery residency training in 1995, he was a research associate in the laboratory of Dr. Bernard Roizman at the University of Chicago (1995-1996) in the area of molecular virology. In 1996, he became full time faculty at the University of Alabama at Birmingham, serving as an Assistant Professor of Surgery in the Division of Neurological Surgery.

Dr. Markert has been involved in the teaching and training of a variety of graduate students, medical students and residents since joining the faculty. In 2000, Dr. Markert was promoted to Associate Professor of Neurosurgery and received a secondary appointment to the Department of Physiology and Biophysics in 2001. In 2003, he received a secondary appointment to the Department of Pediatrics, and in 2004 was promoted to Professor of Neurosurgery. Subsequently he received an appointment in the Department of Cell Biology. In 2006, he was appointed Director of the UAB Division of Neurosurgery, and has increased the faculty to a total of 19, with 3 new research faculty. He recently served as the President of the Southern Neurosurgical Society and has served as Scientific Program Director for both the Academy of Neurological Surgeons and the Society of Neurological Surgeons. He is on the faculty of the UAB CCC, the Gene Therapy Center, and the Minority Health and Research Center. Dr. Markert lectures in the Neuropathology Course for the second year medical students each year as well as lecturing in the Spirituality and Medicine course, also offered by the Medical School. He also serves as a faculty lecturer in the Brain Tumor Biology Advanced Course**. Dr. Markert is an active mentor for numerous Neurosurgery Residents and graduate students.**

Dr. Markert has been continuously funded as principal investigator on NIH grants since receiving his first award, a K08, in 1996. His mentors for this grant included Dr. Richard Whitley and Dr. Yancey Gillespie, two of the faculty mentors on this current training grant application. He has been extremely active as an invited lecturer at national meetings, international meetings, and as a visiting professor. Dr. Markert has published over **75** original research papers, review articles, monographs, and book chapters. He also served as chief editor on a special double edition of the *Cancer Journal* devoted to Glioblastoma Multiforme. He is Chief Editor of a book entitled "Glioblastoma Multiforme". He has served as associate editor for *Select Reviews in Neuro-oncology* and as a reviewer for many journals including *JAMA*, *Cancer Research*, *Clinical Cancer Research, Cancer Letters*, *Journal of Gene Medicine*, *Cancer Gene Therapy*, *Frontiers in Bioscience*, *Current Gene Therapy*, *Medical Gene Therapy*, and *Neurosurgery*. Dr. Markert has served on a variety of NIH Special Emphasis Panels and Program Project Cluster Review Panels including the evaluation of program project grants and brain tumor centers.

3B. Administrative Structure and Responsibilities



T32 Executive Committee. Drs. Benveniste, Carroll, and Markert will be responsible for the oversight of the entire program, including fiscal matters, recruiting, quality assurance and improvement, selection of trainees, assessment of trainees performance, and coordination of the program. **An Executive Committee composed of four program faculty (Drs. Nabors, Sontheimer, Bredel and Gillespie), in conjunction with Drs. Benveniste, Carroll and Markert, will oversee the recruitment and acceptance of trainees**. The responsibilities of the Executive Committee include (a) guiding the program in applicant selection, (b) reviewing the individualized training programs for each trainee, including didactic course work, (c) participating in the interdisciplinary program experience, (d) reviewing applications from prospective mentors, (e) guiding the mentoring of mentors, and (f) evaluating progress on the individual mentored research project. The Executive Committee and Drs. Benveniste, Carroll, and Markert will meet twice per year to review the training program and progress of the trainees.

T32 Internal Advisory Board. The Internal Advisory Board (see Schematic) includes experts in clinical and basic science, and in the training of predoctoral and postdoctoral fellows. **Dr. Robert Kimberly** is the Howard L. Holley Professor of Medic pine, Director, UAB Arthritis and Musculoskeletal Center, and Senior Associate Dean for Biomedical Research. Dr. Kimberly has mentored a large number of pre- and postdoctoral fellows. In addition, Dr. Kimberly directs an NIH Institutional Training Grant entitled, "Training Program in Rheumatic Diseases Research". As such, he brings significant administrative and scientific leadership expertise to the Internal Advisory Board. **Dr. James Bonner** is the Chairman of the Department of Radiation Oncology, which has made substantial investments in recruitment of new faculty with

expertise in brain tumor biology in the recent years (Drs. Bredel and Willey). Dr. Bonner's superb administrative and scientific talents will be an asset to the Internal Advisory Committee. **Dr. David Standaert**, John N. Whitaker Professor and Chairman of the Department of Neurology, was appointed Chairman in 2011, and was recruited to UAB in 2007 as Director, Center for Neurodegeneration and Experimental Therapeutics, Director of the Division of Movement Disorders and Vice-Chair of Neurology. Dr. Standaert is an internationally recognized expert in movement disorders, and heavily involved in NIH-sponsored studies for Parkinson's disease. He is an enthusiastic supporter of the Neuro-Oncology Program, and has committed significant resources for the recruitment of academic neuro-oncologists with basic and/or translational research programs to UAB. **Dr. Lisa Schwiebert**, Associate Dean, Office of Postdoctoral Education, has been instrumental in enhancing the opportunities available for postdoctoral fellows at UAB. She has implemented numerous new courses to aid postdoctoral fellows in their research activities, grant writing activities, and interview skills. Dr. Schweibert serves as Director of the UAB Mentored Experiences in Research, Instruction and Teaching Program (**MERIT***).* This NIH sponsored program is to support postdocs interested in combining research and teaching experiences. As a partnership with historically black institutions to help developing scientists conduct high-quality research in an academic environment, the long-term objectives of this training mechanism seek to enhance research-oriented teaching at minority-serving institutions, to promote interactions between research-intensive universities such as UAB and minority-serving institutions that lead to collaborations in research and teaching, and to increase the number of well qualified, under-represented minority students entering competitive careers in biomedical research. Thus, Dr. Schwiebert will be invaluable in helping the T32 leaders with issues related to under-represented minorities. The combined expertise of the four Internal Advisory Board members will be instrumental in terms of assisting in the development of the Training Program in Brain Tumor Biology, and providing oversight. On an annual basis, the Internal Advisory Board will review the applicants and their proposed projects as presented by Drs. Benveniste, Carroll, and Markert, and provide oversight for the entire program. See **letters of support** at end of Research Training Program Plan.

Specific Administrative Responsibilities. Dr. Etty (Tika) Benveniste, Program Director, is responsible for the overall direction of this training program. She is assisted on a regular basis by Drs. Jim Markert and Steve Carroll, the Program Co-Directors, and by members of the Executive Committee and Program Faculty. In addition, Dr. Benveniste works with Dr. Peter Burrows (Immunology Theme), Dr. Michelle Fanucchi (Pathobiology and Molecular Medicine Theme), Dr. Brad Yoder (Cell, Molecular and Developmental Biology Theme), Dr. Lori McMahon (Neurosciences Theme), Dr. Rosa Serra (Cancer Biology Theme) and Dr. Robin Lorenz (MSTP) in the recruitment of predoctoral students interested in brain tumor biology to UAB. Dr. Benveniste calls meetings of the Executive Committee, of the Program Faculty Committee, and of the Internal Advisory Committee. She prepares the annual report for the T32 Advisory Committee and works with her administrative staff to fulfill all reporting responsibilities of the program. Ms. Rene Eubank is responsible for assistance in the administration of the training program, in the coordination of meetings both for trainees and for program faculty, and in the preparation of the annual reports. Additional assistance is provided by Mr. Alex Boles for financial management of the Training Program.

3C. Program Faculty

FACULTY MEMBER	PRIMARY AFFILIATION	ROLE
Benveniste, Etty (Tika), Ph.D. Professor and Chairman	Cell, Developmental and Integrative Biology	Director and Preceptor
Bredel, Markus, M.D., Ph.D. Associate Professor	Radiation Oncology	Preceptor
Britt, William J., M.D. Professor	Pediatrics	Preceptor
Buchsbaum, Donald J., Ph.D. Professor	Radiation Oncology	Preceptor
Carroll, Steven L., M.D., Ph.D. Professor	Pathology/Neuropathology	Co-Director and Preceptor
Cassady, Kevin, M.D. Associate Professor	Pediatrics	Preceptor
Fiveash, John, M.D. Professor	Radiation Oncology	Preceptor
Gillespie, Yancey G., Ph.D. Professor	Surgery/Neurosurgery	Preceptor
Griguer, Corinne, Ph.D. Assistant Professor	Surgery/Neurosurgery	Preceptor

King, Peter H., M.D. Professor	Neurology	Preceptor
Markert, James M., M.D., MPH Professor	Surgery/Neurosurgery	Co-Director and Preceptor
Nabors, Burton L., M.D. Professor	Neurology	Preceptor
Roth, Kevin A., M.D., Ph.D. Professor and Chairman	Pathology	Preceptor
Sontheimer, Harald W., Ph.D. Professor	Neurobiology	Preceptor
Whitley, Richard J., M.D. Professor	Pediatrics	Preceptor
Willey, Christopher, M.D., Ph.D. Assistant Professor	Radiation Oncology	Preceptor
Zinn, Kurt R., DVM, Ph.D. Professor	Radiology	Preceptor

Description of the Faculty. When the Training Grant was originally funded in 2007, there were 16 preceptors. Of those 16, 1 is deceased (Dr. D. Benos), 1 retired (Dr. R. Kaslow) and 2 left UAB for other institutions (Drs. X. Chen and C. Gladson). Three additional preceptors were added over time (Drs. D. Curiel, F. Lin and J. Parker). Dr. Parker has retired, and Drs. Curiel and Lin went to other institutions. Of the current 17 preceptors, 12 were on the original grant (Benveniste, Britt, Buchsbaum, Carroll, Gillespie, King, Markert, Nabors, Roth, Sontheimer, Whitley and Zinn). Of the 5 new preceptors, 3 were newly recruited to UAB (Bredel, Griguer and Willey), and 2 UAB faculty were added due to their involvement with brain tumor biology (Cassady and Fiveash). These preceptors have been chosen due to their strong basic science and/or translational research programs as related to brain tumor biology. Included are faculty members at the ranks of Assistant (2), Associate (2) and Full (13) Professors with strong track records in training graduate students/postdoctoral fellows/residents, teaching activities, and research experience. The Program Faculty includes senior investigators with well-established research programs as well as highly effective younger investigators (e.g., Drs. Bredel, Cassady, Griguer and Willey). The Program Director, Co-Directors and Executive Committee believe that participation of younger faculty members in this training program is important for the development of both faculty and trainees. The role of the Program Faculty is (a) to assist in the recruitment of predoctoral students and postdoctoral fellows, (b) to discuss their research at appropriate forums designed for both pre- and postdoctoral trainees, (c) to make their laboratories and research teams available for rotations, (d) to serve as a preceptor for research projects, (e) to provide timely feedback about progress to the Program Director, Co-Directors and Executive Committee, and (f) to assist trainees in planning for their future career. The research interests, extramural grant support, training grant participation, and training records of the Program Faculty are provided in **TABLES 2-5A/B**. The preceptors associated with this training program are competitive in obtaining research support as evidenced by the large number of active grants held by the faculty (**TABLE 4**). This will ensure a stable training environment and that the trainees are exposed to strategies used by the faculty to effectively and efficiently fund their research. The preceptors also have been selected on the basis of their expertise in both selecting candidate trainees with the potential for success in this field of research, and their ability to groom their trainees for independent and productive careers in academic research. Moreover, the number of preceptors will ensure that in any one year, the program can find an appropriate "match" for the very best candidate trainees, thus promoting the excellence of the candidate pool. Descriptions of faculty research interests are listed below, as well as collaborators.

Etty (Tika) Benveniste, Ph.D. Dr. Benveniste's research is focused on the contribution of **aberrantly activated signaling pathways** to the growth and development of GBMs. In particular, two pathways, **the JAK/STAT and NF-κB pathways**, are hyper-activated in GBMs due to the loss of negative regulators such as PIAS3 and ING4, and over-expression of activators such as Casein Kinase 2 (CK2), Pin1, IL-6 and TNF. We are examining how these pathways contribute to the mesenchymal subtype of GBMs, their activation status in glioma-initiating stem cells, and the cross-talk between the pathways. Using a variety of GBM animal models, we are testing pharmacological inhibitors of some of these pathways and molecules. These include AZD1480, a JAK1/JAK2 inhibitor; CX-4945, a specific inhibitor of CK2; and BAY-11, a NF-κB inhibitor. These drugs are being used individually and in combination. Thus far, the results with AZD1480 and CX-4945 are very promising *in vivo*, demonstrated efficacy in hitting their targets, and promoting survival of mice with intracranial human GBM primary xenografts. We believe these studies have direct relevance for the treatment of patients with GBMs. These studies are being conducted in collaboration with Drs. Gillespie, Bredel and Nabors.

Markus Bredel, M.D., Ph.D. The brain and its maladies are ever mysterious but more easily treatable than they used to be, except for brain tumors whose prognosis remains mostly dismal. **Our laboratory is dedicated to understanding the genetics of brain tumors with a particular focus on human gliomas.** This incredibly challenging disease highlights both the application of cutting edge scientific medicine and its limitations as these tumors evade the most targeted therapies. Our work integrates complex molecular tumor data generated by the complementary and iterative application of data-driven (**systems biology**) and hypothesis-driven research approaches and corresponding clinical patient profiles. Our focus lies on the deregulation of signaling pathways that result in tumorigenesis and treatment resistance. We combine complex genomic network analysis from patient tumor samples with both *in vitro* and *in vivo* models to identify new therapeutic strategies. We also aim to use **tumor profiling and genomic analyses** to benefit the patient in providing prognostic information and aiding in therapeutic decision-making. Our lab is highly collaborative in nature as we work within the neuro-oncology field to offer patients new hope, educate and train the next generation of neuro-oncology scientists, and advance the general body of knowledge concerning the origins and nature of brain tumors. Collaborators include Drs. Fiveash and Benveniste.

William J. Britt, M.D. The focus of my laboratory is the **study of the biology of the interaction between large DNA viruses, primarily cytomegaloviruses, and the host.** We have initiated several projects directly related to the **potential role of these agents in promoting the neoplastic behavior of gliomas.** These studies deal specifically with the capacity of CMVs to induce wound-healing behavior such as cellular migration and angiogenesis in a variety of cells, including glioblastoma cells and normal glial cells. Our goals are to relate virus-encoded functions to specific cellular activities by dissecting the mechanism of action of specific viral genes that lead to cellular responses such as migration. We believe that such perturbations in normal cellular functions could provide a potential mechanism for the role of DNA viruses in the malignant behavior of locally invasive tumors such as glioblastomas. Collaborators include Dr. Cassady.

Donald J. Buchsbaum, Ph.D. My recent research involves the use of **agonistic TRAIL receptor binding antibodies** in combination with chemotherapy or radiation therapy in orthotopic and metastatic breast, pancreatic, **glioblastoma**, and ovarian cancer models. These studies are in collaboration with Drs. Gillespie, Fiveash, Willey, Whitley, Zinn and Markert.

Steven L. Carroll, M.D., Ph.D. The Carroll laboratory is focused on determining what molecular abnormalities are responsible for the development of **schwannomas, plexiform neurofibromas and malignant peripheral nerve sheath tumors (MPNSTs)** and using this information to develop effective new treatments for these neoplasms. We have found evidence that abnormal signaling by neuregulin-1 (NRG1) promotes the pathogenesis of these peripheral nerve sheath tumors in humans. We have developed a novel genetically engineered mouse model in which inappropriate expression of NRG1 in Schwann cells results in the development of large numbers of plexiform neurofibromas that progress to become MPNSTs at a very high frequency. This animal model gives us a unique opportunity to establish both what abnormalities drive the development of plexiform neurofibromas, and to determine what subsequent changes cause plexiform neurofibromas to undergo malignant transformation.

We are using additional novel mouse models and other approaches to **identify therapeutic targets within key signaling pathways regulated by NRG1**. We have identified three novel classes of compounds that effectively inhibit the growth of plexiform neurofibromas and MPNSTs in culture—we are now testing the effectiveness of these compounds in our genetically engineered mouse model and in mice that have been grafted with human tumor cells. To identify even more therapeutic targets in NF-associated peripheral nerve sheath tumors, we are also using cutting-edge high throughput sequencing methods to comprehensively identify all of the genetic changes (mutations) and epigenetic abnormalities driving the development of peripheral nerve sheath tumors; these studies are being performed using tumors collected from human NF patients, tumors developing in our NRG1 overexpressing mouse model and tumors occurring in *Nf1* knockout mouse models. These comprehensive approaches thus continue to identify potential new treatment targets, thereby laying the groundwork for the development of effective new therapies for NF-associated tumors. Active collaborators include Drs. Roth, Markert and Zinn.

Kevin Cassady, M.D. My research focuses on the pathogenic mechanisms by which Herpes Simplex Virus (HSV) and Human Cytomegalovirus (HCMV) evade innate immune recognition in infected cells. Specifically we are investigating how HSV induces interferon signaling within the initial hours of infection and how interferon induced antiviral genes limit viral replication and neurovirulence. In addition to these intracellular antiviral responses, we are also investigating how HSV down-modulates cell surface receptors during infection in order

to avoid innate immune cell detection. **Defining the genetic mechanisms enabling viral evasion of the host antiviral defense has allowed us to develop an avirulent HSV/HCMV chimeric virus as an anti-tumor therapeutic.** Preclinical studies show that the chimeric HSV is superior to existing HSV oncolytic viruses. The chimeric HSV is under patent protection and through an NCI RAID award, clinical grade virus is currently being manufactured. Through recent SPORE funding, **we are advancing the chimeric HSV to Phase I clinical trial for patients with Glioblastoma.** This work is in collaboration with Drs. Markert, Whitley and Gillespie.

John Fiveash, M.D. Dr. Fiveash has been an active educator and researcher in brain tumors for over thirteen years. He currently serves as the Residency Director and Vice Chair for Radiation Oncology and led an expansion and transition in the curriculum to include two training curricula: 1) Holman Pathway, an alternative translational oncology training program; and 2) the clinical trials training program. He has mentored medical students, graduate students, fellows, and residents in performing clinical and translational research. In the UAB Comprehensive Cancer Cancer, he serves as the Associate Director for Clinical Research and is a Project Co-leader in the UAB Brain Tumor SPORE. **Dr. Fiveash's long-term career goal is to mentor others in translational and clinical research for brain tumors.** His collaborators include Drs. Buchsbaum, Nabors, Bredel and Gillespie.

G. Yancey Gillespie, Ph.D. Dr. Gillespie serves as Program Co-leader for the Neuro-Oncology Program in the Comprehensive Cancer Center and is Director of the UAB Brain Tumor SPORE. His research interests fall into two general areas, both of which involve strategies to develop and test specific therapies for treatment of malignant primary brain tumors in adults and children. The primary focus is on **oncolytic virotherapy**, involving two different large DNA viruses: adenovirus and herpes simplex virus. The major focus is development and characterization of replication conditional viruses (HSV-1, Ad) that are both oncolytic for glioma cells and express foreign therapeutic genes. Gene transfer includes both pro-drug converting enzymes and cytokines under different promoter systems. The ability of conventional therapeutics (radiation, chemotherapy) to enhance the replication and spread of HSV throughout the tumor mass is being applied at the cellular and molecular levels to determine how it can be best exploited as a multi-modality therapeutic strategy. Findings are validated by *in vitro* assays before being advanced to safety and efficacy assessment in a variety of murine models of intracranial malignant gliomas. Our models include transplantable intracranial gliomas of human origin (in immunocompromised nude mice) or mouse origin (in syngeneic conventional mice). Over 30 human glioma "xenolines" have been established and maintained by serial passage in nude mice. These have been genomically, transcriptomically and kinomically characterized. The second focus is on **glioma stem cells**, thought to be responsible for maintaining the neoplastic clone. These are being isolated and characterized with regard to their enhanced ability to resist infection and replication of oncolytic armed viruses. As an adjunct to virus-based therapeutics, small molecules that exert an anti-angiogenic effect on tumor neovasculature or that induce apoptosis in human glioma cells are being studied as co-therapeutic agents *in vitro* and in animal models of malignant brain tumors. Dr. Gillespie has numerous collaborators, including Drs. Markert, Whitley, Buchsbaum, Cassady, Nabors, Benveniste, Fiveash, Griguer, King and Willey.

Corinne Griguer, Ph.D. My research interests center on **bioenergetics pathways involved in the development and progression of malignant glioma**, and translating findings from benchtop to bedside. Two main topics are studied in my laboratory: the role of mitochondrial bioenergetics in chemoresistance and the role of mitochondria in stem cell biology. My laboratory uses complementary approaches including molecular, cellular biology techniques to study mitochondria from cell lines to human glioma biopsies. My long-term goal is the development of novel and less toxic therapeutic agents, and understanding the molecular mechanisms to improve outcomes of current agents and therapies. Collaborators include Drs. Gillespie and Markert.

Peter King, M.D. My laboratory focuses on **mechanisms of post-transcriptional gene regulation in glioma tumors.** Many of the growth factor mRNAs critical to glioma tumor progression, including VEGF, COX-2, IL-8 and TNF, contain AU-rich elements in the 3'UTR that govern transcript half-life. Stabilization of these mRNAs leads to enhanced expression of these growth-promoting genes, thereby promoting the malignant phenotype (growth and angiogenesis). We are analyzing the cellular factors that interact with the 3'UTR, and how the resultant ribonucleoprotein complexes lead to this stabilization. This molecular pathway is likely a suitable target for anti-tumor therapy, since RNA stabilization is preferentially activated in cancer cells versus quiescent, normal cells. Our long-term goal is to develop small molecules that disrupt "stabilizing" ribonucleoprotein complexes, thus preventing the upregulation of growth genes in gliomas. These studies are in collaboration with Drs. Nabors and Gillespie.

Jim Markert, M.D., MPH, has major laboratory and clinical research interests in the development of novel treatments for brain tumors utilizing molecular biology, viral vectors, and gene therapy. **His current laboratory research focuses on engineered HSV-1 as a vector for immunologic (e.g., cytokines and cell surface antigens) and anti-angiogenic means of treating primary and metastatic central nervous system neoplasms.** Dr. Markert's laboratory also examines the biologic effects of HSV-1 treatment in human tumor and clinical specimens from clinical trials. His major intererst in is gliomas, but has also studied the impact of these vectors in other neoplasms. Most recently, he and Dr. Carroll have begun a joint research effort examining the impact of these vectors in Malignant Peripheral Nerve Sheath Tumors. Collaborators include Drs. Whitley, Cassady, Carroll, Gillespie, Buchsbaum and Griguer.

L. Burton Nabors, M.D. My research efforts are focused into three major areas. The first is a basic effort to understand the role post-transcriptional processes play in cancer initiation and progression. I am investigating the role of **post-transcriptional regulation of gene expression in primary brain tumors**. I am focused on growth factors, cytokines, and regulatory genes involved in proliferation, survival, angiogenesis and invasion. RNA stabilization is an emerging area of importance in the control of mRNA levels. I am interested in factors important in stabilization (RNA-binding proteins) and the signaling pathways which control this level of gene regulation. The second area of research interest takes advantage of my engineering background and appointment in the School of Engineering. We are interested in the **acquisition and post-processing of magnetic resonance imaging data in patients with primary brain tumors.** We are particularly interested in the utility of perfusion and diffusion tensor imaging as non-invasive modalities to evaluate tumor angiogenesis, proliferation, and invasion. This effort compliments our early phase evaluation of novel glioma therapies. The third area of interest is the logical extension of the first two for a physician-scientist and involves the **early phase clinical evaluation of novel cancer therapies.** This includes the design and implementation of trials for newly diagnosed and recurrent malignant glioma that utilize biologically targeted strategies and includes non-invasive endpoints in the evaluation of a biological effect. These studies are in collaboration with Drs. King, Benveniste, Gillespie, Markert, Whitley and Sontheimer.

Kevin Roth, M.D., Ph.D. My research focuses on the **molecular regulation of neuronal cell death**. The goal is to understand the role of cell death in nervous system development and its significance in neuropathological conditions including nervous system neoplasia. We are developing therapeutic approaches that target both apoptotic and autophagic death pathways. Dr. Roth collaborates with Drs. Carroll.

Harald W. Sontheimer, Ph.D. Our lab studies the **mechanisms that allow glial cell migration during development, after injury and in malignancy, particularly the intrinsic adaptations that facilitate cell shape changes during migration.** We recently discovered that the secretion of chloride through ion channels is an essential component for the invasion of glioma cells, and a pharmacological chloride channel inhibitor is currently being evaluated clinically. We are using a variety of techniques ranging from molecular biology, confocal and fluorescent cell imaging techniques to patch-clamp electrophysiology and a variety of cell migration/invasion models. We are routinely comparing properties of normal glial cells to glial cells associated with nervous system diseases, employing primary cells and tissues derived from biopsies of patients presenting with glial tumors or other nervous system diseases. These studies are in collaboration with Dr. Nabors.

Richard J. Whitley, M.D. Dr. Whitley's research group focuses on the **translation of the molecular biology of herpes simplex virus (HSV) to clinical application in the treatment of brain tumors**. HSV has been engineered to: 1) express foreign genes that promote tumor destruction upon intratumoral inoculation and 2) generate viruses that can be administered intravenously which home to brain tumors. Animal models serve as a mechanism to define proof of principle. Successfully engineered viruses include one that expresses IL-12, which is currently under review by the FDA for upcoming use in clinical trials. Collaborators include Drs. Markert, Gillespie, Cassady, Buchsbaum and Nabors.

Christopher Willey, M.D., Ph.D. My research interests in brain tumor biology are predominantly related to cellular signaling. I have particular interest in **global kinase signaling cascades** as well as specific interest in phospholipid pathway signaling. My work has focused on GBM models including immortalized GBM cell lines, patient-derived GBM tumor xenolines, as well as human tumor analysis from databases and archived tissue banks. A major research effort for my lab is the profiling of global kinase activity (kinomic profiling) in these models. I am the director of the UAB Kinome Core which utilizes the PamStation®12 high-content peptide microarray platform (PamGene BV, The Netherlands) to survey kinome activity within cell and tissue lysates. This kinomics system is being used to characterize glioblastoma models in collaboration with Yancey Gillespie,

PhD. We are integrating kinomics data with other high content data sets including genomic and transcriptomic data for several investigative purposes, including hypothesis generation, building classifiers of tumor biology and treatment response, and modeling/comparison to patient data. We are now using these data for potential personalized medicine strategies in GBM.

The other major project relates to phosphatidyl-inositol phosphate **(PIP) signaling in GBM models**. PIPs control the activation of important kinases that drive GBM proliferation and treatment resistance including Akt and Bmx kinases. One potential regulator of PIPs is the protein Myristoylated Alanine Rich C-Kinase Substrate (MARCKS). We have found that the MARCKS protein can regulate glioma growth and radiation sensitivity from our studies of immortalized GBM cell lines, GBM xenolines and analysis of the REMBRANDT and The Cancer Genome Atlas (TCGA) databases. Currently, we are investigating the mechanisms by which MARCKS controls GBM proliferation, senescence, DNA repair, and migration. Dr. Willey is collaborating with Drs. Gillespie, Bredel and Buchsbaum.

Kurt R. Zinn, DVM, Ph.D. Our research focuses on the development of imaging approaches that can monitor molecular events in small animal models. In particular, technologies that have the potential to translate to human applications are emphasized. **Our research emphasizes the development of imaging methods (PET, MR, and ultrasound) to detect cancer, and to determine when cancer therapy is effective.** Using MR diffusion-weighted (DWI) and perfusion imaging we are able to detect effective cancer therapy within a few days after the therapy is initiated. The imaging approaches have been translated to human testing, including "Abraxane With or Without Tigatuzumab in Patients With Metastatic, Triple Negative Breast Cancer" with DWI and DCE-MR imaging to evaluate early response to therapy, and "Phase I Trial of Intraperitoneal Pb-212-TCMC-Trastuzumab for HER-2 Expressing Malignancy with high resolution gamma ray spectroscopy for imaging Pb-212 and daughters. Similar PET-based approaches are being tested to follow mouse models of glioma. Collaborators include Drs. Carroll and Buchsbaum.

Collaborations and Interactions. The Program Faculty have been selected based on their interests in topics directly relevant to the study of brain tumor biology and treatment, as well as their collaborative interactions, as described above. These collaborations are evident in the joint mentorship of our trainees, in collaborative projects and grants, and co-authorship amongst our training faculty *and* trainees (see **TABLES 4, 6A and 6B** and **APPENDIX F**). These findings demonstrate the fruits of the prevailing spirit of collaboration at UAB, and document that our program has a strong tradition of joint mentorship of our trainees.

Mentoring of Mentors. UAB undertook an institutional commitment to enhance the postdoctoral experience through the creation of the OPE in 1999 (**APPENDIX B**). The success of this commitment was nationally recognized when in both 2010 and 2011, UAB was ranked among the top 10 Universities for Postdocs by The Scientist Magazine. Further, to re-shape the predoctoral program and to enhance the predoctoral experience, UAB recruited Dr. Susan Rich and Dean Bryan Noe to the Graduate School in 2004. Both initiatives have emphasized the importance of mentoring and mentoring skills. The Program Director, Co-Directors and Executive Committee recognize that nurturing the mentoring skills of our younger faculty (Bredel, Cassady, Griguer and Willey) is vital. Drs. Benveniste and Gillespie serve on a Mentoring Committee for Dr. Willey, and have been impressed with his growth as a Mentor for predoctoral/postdoctoral fellows in his lab. Drs. Benveniste and Carroll will form a Mentoring Committee for Dr. Griguer when she accepts trainees in her lab. During the meetings of the Program Faculty, issues of effective mentoring are reviewed and discussed. Furthermore, trainees are asked to evaluate their mentors as part of the ongoing facilitation of the overall training program. Each trainee and his/her mentor are asked to create written goals including courses, conferences, and the mentored research project. These goals form the basis for evaluation of progress, both of the trainee and of the mentor/trainee relationship. As a resource for mentors, the program provides the monograph, "Adviser, Teacher, Role Model, Friend: On Being a Mentor to Students in Science and Engineering" (National Academy Press, 1997) as well as "A Guide to Training and Mentoring in the Intramural Research Program at NIH" "On the Right Track: A Manual for Research Mentors" (Council of Graduate Schools, 2003) and "Making the Right Moves: A Practical Guide to Scientific Management for Postdocs and New Faculty" (Howard Hughes Medical Institute, 2004).

3D. Proposed Training Program

Overview. Guided by our experience in the previous funding period, we have crafted a two-year program of research and education for the trainees supported by this Training Grant. The overall training program is comprised of two components: a didactic curriculum and a mentored, investigative

research project. Elements appropriate to each predoctoral and postdoctoral trainee are selected according to their individual training goals and research interests.

The didactic curriculum is built upon five Thematic Programs in the Graduate Biomedical Sciences (**APPENDIX A1-A6**). Basic science predoctoral students accepted by GBS rotate through laboratories during their first graduate year with the goal of selecting a mentor and laboratory by the end of the first graduate year. MSTP students (**APPENDIX A7 and A8**) also take part in three rotations. The first begins in June prior to entry into the first medical school year. The second and third occur during the next two summers, after which they choose a mentor and laboratory at the start of their first graduate school year. Both the GBS and the MSTP programs provide extensive training in the scientific method and expose trainees to a broad range of current approaches used in modern biomedical and translational sciences. The curriculum for the Thematic Programs, (**APPENDIX A**) also provides the framework for formal instruction for postdoctoral trainees wishing to expand their knowledge base in the biomedical sciences pertinent to brain tumor biology research.

All trainees are required to enroll in the **Advanced Course in Brain Tumor Biology**, and participate in two new courses, the **Brain Tumor Clinical Course** and **TCGA/Bioinformatics Tutorial,** which are described in more detail later. In addition, trainees participate in the **Interdisciplinary Enrichment Program** comprised of 1) luncheons with visiting seminar speakers (Brain Tumor Research Seminar Series-held monthly), 2) the monthly Research-In-Progress Brain Tumor Conference, and 3) the Annual UAB Brain Tumor SPORE Scientific Retreat. Through these mechanisms, there is much opportunity for networking with leaders in the field of Brain Tumor Biology, and the formation of beneficial collaborations.

When postdoctoral trainees are in their second year of support on the Training Grant, they enroll in the Grant Writing Course for Postdoctoral Scholars offered by the OPE (**APPENDIX B8**). The trainees write six page grants focused on hypothesis, significance, innovation and approach. After an oral presentation and questions, each grant is then thoroughly discussed by the class in the form of a study section. The ultimate expectation is for each trainee to submit their grant proposal for external funding. **This process has resulted in two of our postdoctoral trainees, Drs. Braden McFarland and George Dobbins, successfully competing for Individual Postdoctoral Fellowships.**

Objectives. The primary objectives of this training grant are three-fold: 1) to develop experimental competence in our trainees such that they become independent and productive investigators; 2) to develop the necessary skills in our trainees such that they can evaluate critically their own experimental data and that of other investigators; and 3) to familiarize trainees with the many modern tools of molecular-based research that are available in our laboratories, and to encourage collaboration and cooperation in solving experimental problems. **The overall objective of this grant is to produce a cadre of talented and ambitious researchers to further our understanding of the biology of brain tumors, and to develop new and effective approaches to treatment**.

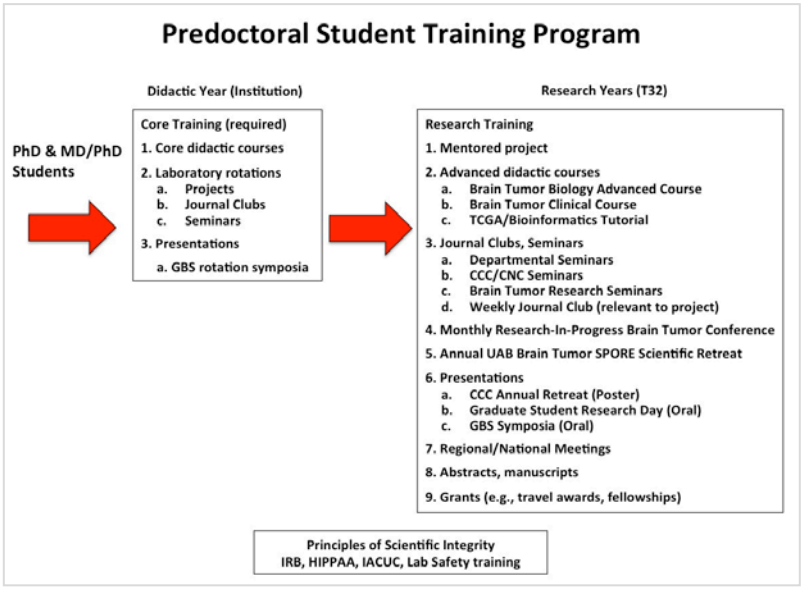
We will structure a two-year period of research and education for each of the pre- and postdoctoral trainees on this training grant. Predoctoral students (PhD and MD/PhD) select their thesis project and laboratory(ies) based on their rotation experience with guidance from GBS advisors. A predoctoral trainee will be required to have successfully completed the first year of graduate work (didactic courses and lab rotations) as well as have one year of laboratory research training experience before being considered for a position on this training grant. Postdoctoral trainees will be considered for a position on the training grant in their first, second or third year of postdoctoral training. Special consideration will be available for postdoctoral applicants past the third year of postdoctoral training who are applying for a position on the training grant from a clinical training position (e.g., residency). Postdoctoral applicants with Ph.D., M.D., D.D.S., or D.V.M. degrees will be considered. The time period on the training grant will be limited to two years, and all awardees will be strongly encouraged to submit individual pre- and postdoctoral NIH fellowship applications, or fellowship applications to other appropriate funding agencies. The training grant positions will be awarded on a competitive basis, based on the applicant's coursework GPA, a two-page grant proposal, the number and quality of publications (especially relevant for postdocs), the mentor's experience and expertise in the area of research, and the likely success of the applicant. **We will strongly encourage and solicit applications from under-represented minorities, persons with disabilities and women**. The Executive Committee, in conjunction with Drs. Benveniste, Carroll, and Markert, will be responsible for selecting trainees for this program.

Didactic Coursework (Predoctoral Trainees). Predoctoral trainees are accepted into this training program only after having completed their second year of graduate school. The predoctoral trainees affiliated with this training grant are expected to fulfill the requirements for advanced courses, journal clubs, presentations and

publications as dictated by their particular Thematic Program (see **APPENDIX A1-A6**). All Thematic Programs require a Biostatistics Course and a Grant Writing Course. The predoctoral trainees will be required to take the **Brain Tumor Biology Advanced Course** as one of their advanced courses, and a weekly journal club in relevant areas of biology (examples include Mechanisms of Signal Transduction, Cell Cycle Regulation and Cancer, Cancer Genetics, Cancer Cell Biology, and Diseases of the Nervous System)**.** In addition, the predoctoral trainees will take the **Brain Tumor Clinical Course** and the **TCGA/Bioinformatics Tutorial**.

Didactic Coursework (Postdoctoral Trainees). The postdoctoral trainees accepted into the program may have considerable variation in graduate training, particularly those accepted from a clinical training position. Thus, formal coursework will be necessary for the postdoctoral trainees. They may participate in modules of the GBS Thematic Programs, as needed, or take appropriate advanced courses offered by the various departments/programs. **The Brain Tumor Biology Advanced Course, Brain Tumor Clinical Course and TCGA/Bioinformatics Tutorial will be required.** The Directors and the Executive Committee, together with the faculty mentor, will evaluate each postdoctoral trainee for any potential coursework needs before he/she enters the program. A formal recommendation regarding coursework will be given to each postdoctoral trainee; no trainee will be expected to take more than two courses in any calendar year. Every effort will be taken to avoid compromising time for research and individual study.

All trainees are required by the institution to take **GRD 717, Principles of Scientific Integrity (APPENDIX D4**), as well as a rigorous curriculum in the responsible conduct of research, with fundamental requirements in human subjects, vertebrate animal and laboratory research.



Brain Tumor Biology Advanced Course. This semester-long course will be required of all pre- and postdoctoral trainees supported by this training grant. The Brain Tumor Biology Advanced Course has been carefully designed to provide trainees with the information that is essential for their development as brain tumor biologists; although this course has an emphasis on gliomas, we have been careful to ensure that it instills the trainees with an understanding of the other tumor types that are encountered in the human nervous system. The course begins with an introduction to the clinical and pathologic features of nervous system tumors and the molecular and cellular mechanisms that govern the biology of these neoplasms. The role that **cancer stem cells** play in the initial pathogenesis and expansion of nervous system neoplasm and the importance perivascular microenvironments have for these stem cells is presented to the trainees. Given the growing importance of **genomics in cancer biology**, we have taken care to include lectures on brain tumor genetics and **systems biology**. Trainees are introduced to **inflammatory and immune response** alterations that occur in nervous system neoplasms and how these changes impact tumor growth. The mechanisms mediating tumor cell **invasion and angiogenesis** are also considered. Building upon this foundation of basic information, trainees are then taught the proper use of **animal models** of nervous system neoplasms and imaging modalities that can be used to follow tumor responses in preclinical trials. Trainees next proceed to a more clinically oriented consideration of nervous system neoplasms. Working with clinical faculty, they receive training in the **imaging and neuropathology of brain tumors** and the principles underlying conventional and experimental approaches to brain tumor therapeutics. Finally, trainees are taught the principles of **clinical trial design**. Interested trainees may participate in the design of an actual clinical trial as such opportunities are available. This course has been offered since Spring of 2004, and will be offered again in the Fall of 2012. This course has consistently received very favorable reviews of its content and lectures (See **APPENDIX D1 and D2**).

Brain Tumor Clinical Course. The impetus for this new course came from the students/fellows taking the Brain Tumor Biology Advanced Course, in which they indicated a desire to learn more about the clinical aspects of brain tumors, and patient care. This led to the development of the **new** Brain Tumor Clinical Course, which will be part of their formal didactic training. This course will be offered for the first time in

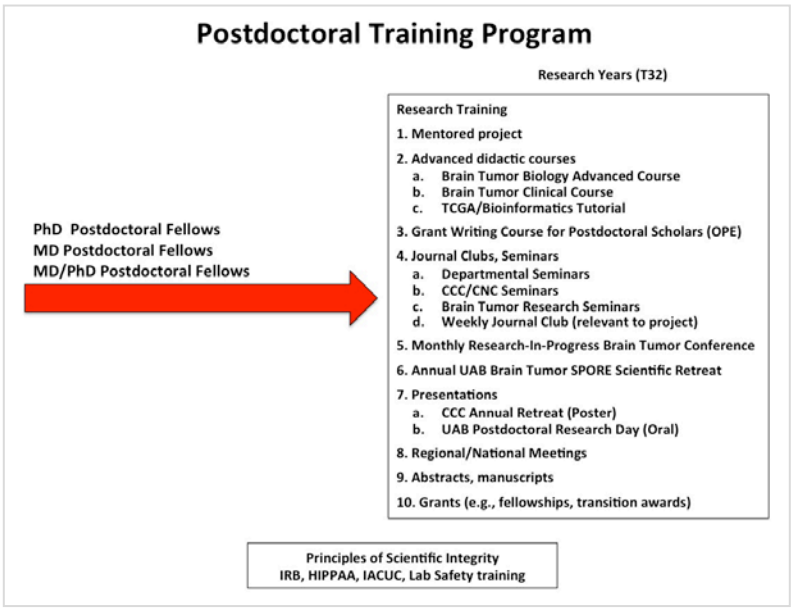
Spring 2013. Trainees will be introduced to the clinical aspects of caring for patients with malignant brain tumors including signs and symptoms, presentation, neurologic findings, appropriate diagnostic workup, interpretation of diagnostic imaging, and typical findings including CT, MRI, Diffusion Tensor Imaging with tractography, magnetoencephalography, and functional MRI scanning. Trainees will also be taught the basics of therapeutic intervention for malignant gliomas as well as the pertinent aspects of decision-making regarding surgical intervention as well as radiation therapy. Interested trainees may participate in surgeries as observers in the operating room. Relevant aspects of recurrence, and approaches to treatment of recurrent tumors using agents such as bevacizumab, as well as clinical trial options in emerging therapies, will also be covered.

The formal portion of the Clinical Course will include participation in **Brain Tumor Board**. This is a multi-disciplinary conference held every Tuesday morning from 7:00-8:00 am. Case presentations are made to a multi-disciplinary group that includes **neurosurgeons, neuro-oncologists, neuroradiologists, radiation oncologists, and neuropathologists.** These presentations assist them in understanding the implications of these aspects of the disease for planning new therapies. **Trainees will be expected to attend Brain Tumor Board once/month for the duration of the time they are on the Brain Tumor Biology Training Grant.** Trainees will learn the fundamental aspects of **Radiation Oncology** approaches to brain tumors through didactic sessions and clinic experiences. The stereotactic radiosurgery conference occurs on Friday mornings at 7:30 in which both gamma knife and linear accelerator-based (LINAC – i.e., Varian True Beam) cases are presented and discussed. **Trainees will attend 4 consecutive Monday (8:00-9:00 am) lectures regarding radiation oncology for central nervous system tumors that occurs in the Spring each year.** Trainees will also participate in **Surgical Neuropathology** conferences. These conferences, directed by Dr. Steven Carroll, are held every Tuesday and Friday from 9:00-10:00 am, and are attended by the neuropathology attending physicians, neuropathology fellows, rotating anatomic pathology residents, rotating neurology residents and medical students. These are working conferences in which the surgical specimens (primarily nervous system neoplasms) coming through the Neuropathology service are reviewed. The Neuropathology conferences additionally serve as teaching conferences in which the Neuropathology attending physicians review the key histologic features of nervous system neoplasms, the molecular abnormalities that underlie the pathogenesis of these tumors and the therapeutic implications these findings have for the patients. As part of this conference, neuroradiology images are also reviewed and correlated with the neuropathologic findings. **Trainees will be expected to attend Neuropathology Conference once/month for the duration of the time they are on the Brain Tumor Biology Training Grant.**

Lastly, trainees will participate in Neurology, Neurosurgery, Radiation Oncology and Neuro-oncology clinics. This will involve a **"shadowing"** process in which trainees attend clinic and have the opportunity to see patient presentations, neurologic findings, and learn about diagnostic and treatment decision making processes first hand, as well as having the opportunity to interact directly with patients and their families. Dr. Markert has clinic on Mondays and Wednesdays and Neuro-oncology clinic is held by neuro-oncologists, including Dr. Nabors, on Mondays, Wednesdays, and Thursdays. Dr. Markert is in the operating room on Tuesdays and Thursdays as well as performing Gamma Knife radiosurgery on Wednesdays. He also performs fractionated stereotactic radiosurgery using the True Beam on an ad hoc basis as necessary. Trainees will work with radiation oncologists, including Drs. Willey, Bredel and Fiveash, in clinical shadowing opportunities and learn how radiation treatment plans are developed for brain tumors. **Individual shadowing experiences will be designed for each trainee based on their particular interests, and will span the two years they are supported on the Training Grant.** The preliminary outline for this course is in **APPENDIX D3.**

"Hands-On" TCGA/Bioinformatics Tutorial. The Cancer Genome Atlas (**TCGA)** began in 2006 with the goal of identifying the changes in each cancer's genome, and to use this information to understand how such changes interact to drive the disease. Ultimately, this information will lay the foundation for improving cancer prevention, early detection and treatment. GBM was the first cancer chosen for study by the TCGA, and the TCGA has achieved comprehensive sequencing, characterization and analysis of the genomic changes in over 500 GBM samples. With the publication in 2008 of TCGA data on GBM, "Comprehensive Genomic Characterization Defines Human Glioblastoma Genes and Core Pathways", Cancer Genome Atlas Research Network, *Nature* (2008) 455:1061-1068, there has been an explosion in this field, and a wealth of data to be garnered from the TCGA database. One of the most important findings to arise from the TCGA data was the documentation of molecular subtypes of GBMs, including Proneural, Neural, Classical and Mesenchymal. **We feel it is critical for our trainees to receive a "hands-on" tutorial on the use of key resources such as TCGA, Rembrandt and Oncomine, and learn how to navigate these databases and the proper interpretation of bioinformatic data. Towards this end, each trainee in the Program will receive a ½ day**

tutorial personalized to their research project to interrogate these databases. Dr. Markus Bredel, a Mentor on the Training Grant, is expert in this topic. As well, Dr. Jonas Almeida was recruited to UAB in Jan. of 2011 to create the **Division of Informatics** in the Department of Pathology, and serve as Director of the Division. Dr. Almeida has published on the use of TGCA to analyze copy number alterations in GBM (*PLoS One*, 2008). Drs. Bredel and Almeida (or other faculty in the Division) will be responsible for providing the personalized tutorials to the trainees, which will be an outstanding feature of their didactic training.



Interdisciplinary Enrichment Program (Predoctoral and Postdoctoral). To facilitate interaction among trainees and to promote interdisciplinary discussion, all trainees will present in a **monthly Research-In-Progress Brain Tumor Conference** scheduled on Tuesdays from Noon to 1:00 p.m. (lunch is provided). The purpose of this conference is to provide a forum for trainees and faculty to present their research proposals or experimental data, and to receive constructive input from others present. This conference will provide a means of keeping abreast of what each trainee is doing. All personnel in the participating laboratories are welcome. We will encourage frequent presentations by our pre- and postdoctoral trainees at this Conference for two purposes. The first is to give the trainees experience in presenting a research proposal and the results of his/her research activities. Second, subsequent discussion of the trainee's presentation allows faculty not directly involved in the research project to provide advice and constructive criticism. **We will expect our trainees to present approximately every 6 months.** Advice from this training faculty and other trainees will be of considerable value in assisting the trainee in achieving a successful completion to their project. In addition, as faculty will also present at this research conference, this will provide a model for the trainees.

Trainees will also participate in a monthly luncheon with visiting speakers for the Brain Tumor Research Seminar Series, and in the Annual UAB Brain Tumor SPORE Scientific Retreat. Attending this retreat will be the External Advisory Committee of the SPORE Grant, comprised of leading experts in Neuro-oncology (Dr. F. Ali-Osman, Duke; Dr. M. Berens, TGen; Dr. W. Debinski, Wake Forest; Dr. C. Gladson, Cleveland Clinic; Dr. S. Piatadosi, Johns Hopkins; and Dr. S. Rosenfeld, Cleveland Clinic). The trainees will have short oral presentations and posters at this retreat. The trainees will also be expected to attend one of the following weekly Departmental seminars; Cell, Developmental and Integrative Biology; Molecular and Cellular Pathology; Neurobiology; and Neurology (see **APPENDIX E** for examples), or seminars hosted by the Comprehensive Cancer Center or the Comprehensive Neuroscience Center. The broad number of excellent seminar series on campus will provide the trainees with exposure to the most advanced approaches for scientific investigation relevant to their research.

In summary, the major features of the didactic and enrichment components of the training program include the following:

• Brain Tumor Biology Advanced Course • **New** Brain Tumor Clinical Course • **New** TCGA/Bioinformatics Tutorial • Advanced Courses (as needed) • Weekly Journal Club (of choice)	• Monthly Research-In-Progress Brain Tumor Conference • Monthly Brain Tumor Research Seminar Series • Weekly Departmental/Center-sponsored Seminar • Annual UAB Brain Tumor SPORE Scientific Retreat

Mentored Research Project (Predoctoral and Postdoctoral Trainees). Having selected a research project, the trainee works in the laboratory of the mentor (required) [and the co-mentor(s) (encouraged)], who assumes primary responsibility for the research plan and training of the trainee. Each predoctoral or postdoctoral trainee has projects that are related to, but distinguishable from, those of his/her immediate mentor to facilitate assessment of progress and the development of an individual research program. During the laboratory experience, trainees are expected to acquire or enhance skills in biochemical, cellular and molecular

techniques. Trainees are encouraged to work with one or more of the Program Faculty for discussion and the acquisition of expertise in specific approaches and technologies, a process that is facilitated by the strong collegial tradition at UAB. Each mentor's laboratory has weekly meetings for review of experimental design, techniques and data assessment and interpretation, which the trainees will participate in. In addition, trainees present their results at the Monthly Brain Tumor Research-in-Progress Conference, which is designed to encourage collegial discussion and to generate additional assistance and collaborations. Thus, through individual mentor/trainee meetings to review methodologies, results and to trouble-shoot problems; through weekly laboratory-based research meetings; and through the Monthly Research-in-Progress Conference, there are multiple avenues for mentors and trainees to seek input to optimize both the training experience and progress on the individual research projects.

Formal Presentation of Results. In addition to semi-formal presentation of research results, trainees are strongly encouraged to present their findings at local, regional, and national meetings. For example, there is the **Annual Comprehensive Cancer Center Scientific Retreat** where trainees present posters, the **Annual UAB Postdoctoral Research Day,** which provides the opportunity for postdocs to do oral presentations, and the **Annual UAB Graduate Student Research Day** (oral presentations). These forums provide the opportunity for trainees to organize and present their research to individuals, both within and outside of their primary field of interest. Together, these poster and platform presentations provide an excellent experience in preparation for presentation at national scientific meetings including the Society of Neuro-Oncology (SNO), American Association of Cancer Research (AACR), and American Society of Clinical Oncology (ASCO). As appropriate, trainees may also present their results at international meetings and will be supported for such presentations by their mentor.

Preparation of Manuscripts and Grants. All trainees are expected to publish their results in peer-reviewed journals as part of their training (**TABLES 6A and 6B**). Continuous review and evaluation of the literature in their specific area is an essential element of the training experience. This is accomplished through extensive reading, journal clubs, and attendance at seminars. In addition to manuscripts, the trainees are expected to work with their mentors to submit at least one grant seeking extramural research support. When appropriate, these grants will provide training support, thus replacing or transitioning support from this training grant to their own independent support, thereby beginning to establish a record of external funding and, for postdoctoral trainees, facilitating transition to Junior Faculty status. While it is the primary responsibility of the research mentors, the Program Directors and Executive Committee recognize the importance of a coordinated effort in identifying the best sources of potential funding, and in planning and aiding the development of grant applications for each individual trainee. As mentioned previously, several of our Postdoctoral Trainees have successfully obtained independent funding.

Mentoring of Trainees for the Future. Trainees are encouraged to attend local, regional, and national scientific meetings, not only for scientific interchange, but also for networking and career visibility. Trainees are encouraged to interact directly with faculty at other institutions, as well as with trainees at other institutions. The OPE has regular seminar programs discussing research opportunities and expectations of individuals as they assume faculty positions. These include lectures in laboratory management and career planning (**APPENDIX B)**. All trainees are encouraged to attend such seminars.

Individual Development Plans (IDPs) for Postdoctoral Trainees. Mechanisms have long been in place for career monitoring and development of predoctoral students. These include the combined efforts of the Department or Theme Graduate Director, the Dissertation Committee, the Mentor(s), and the Directors and the Executive Committee of this training program. However, postdoctoral trainees have been generally more dependent on their mentor. Following the lead of the National Postdoctoral Association, we have recently instituted the use of individual development plans (IDPs) for postdoctoral trainees. These plans provide a mechanism to help the trainees identify and clarify their professional development needs and their career objectives; and to facilitate and structure communication between the postdoctoral trainees and their mentors. The goals of the IDPs are to help each trainee identify and seek out the tools and training necessary to achieve their long-term career interests, and to help the trainees and their mentors come to a common understanding of how best to maximize the benefits of their current efforts. These objectives can be separated into four basic steps for both the trainees and the mentors.

	For the Postdoctoral Trainee	*For the Mentors*
Step 1:	Conduct a self assessment	Become familiar with the opportunities available to the trainee
Step 2:	Survey opportunities with mentor	Discuss opportunities with the trainee
Step 3:	Write an IDP, share the IDP with the mentor, and revise	Review the IDP and help revise
Step 4:	Implement the plan Revise the IDP as needed	Establish regular review of progress and help revise the IDP as needed

In Step 1, the postdoc is asked to assess their skills, strengths and areas that they feel need improvement. The trainee is encouraged to seek the advice of their peers as well as their mentors. Most importantly, the trainee is asked to write down their long-term career objectives. In Step 2, the trainee is asked to meet formally with his or her mentor to discuss career opportunities, identify developmental needs, and prioritize their developmental efforts. In Step 3, the trainee is asked to write a formal IDP. This IDP is intended to help the trainee map out the general path they wish to take in the development of their career, and to help the trainee match skills and strengths with career choice. We anticipate that this will be a document that changes as the trainee progresses through the training program. The specific objectives include a projected date for completion of their post-doctoral education, the identification of specific skills and strengths that need to be developed during the training process, and a definition of the approaches to be taken to obtain needed skills and strengths including coursework, technical skills, teaching and mentor supervision. It is critical that the trainee prepare this mapped path with their mentor. The Directors stand ready to help facilitate and monitor this process. In Step 4, the trainee is expected to put the plan into action, and revise as circumstances and goals change.

The mentor is also required to participate in this process. In Step 1 they are requested to become familiar with potential opportunities for future career advancement that may benefit their trainee. In Step 2 they are expected to discuss the trainee's self-assessment and career goals with the trainee. In Step 3, they are expected to help the trainee prepare the IDP. And in Step 4, they are expected to establish a regular review of the trainee's progress. This process parallels that expected for predoctoral trainees through their dissertation committees, with communications to the Directors and the Executive Committee.

Individualized Trainee Programs. Within the frame of the program outlined above, the specifics are individually tailored for each trainee. Two examples include:

Predoctoral (**David Gaston**). David Gaston was recruited to UAB in 2006 to the MSTP MD/PhD training program. His undergraduate GPA was 3.8, and MCAT score a 36. He pursued the prescribed curriculum of core graduate and medical courses in the MSTP program, and after the required rotations in the first and second year of training, he selected co-mentors Dr. K. Cassady and Dr. R. Whitley (Department of Pediatrics) for his thesis work. David's research is to investigate methods to increase the efficacy of oncolytic HSV-1 virotherapy for malignant glioma. David took the Advanced Course in Brain Tumor Biology in 2009. David joined the Brain Tumor Training Grant in January 2011, and was advised by the Executive Committee to submit an NIH F30 Individual Fellowship. With the guidance of his mentors, thesis committee members, and members of the Training Grant, David submitted his grant in August 2011. The grant received a favorable score of 30, which, according to NCI officials, should be awarded. Due to NCI internal issues, David is still waiting to learn the final decision on his application. David has presented his work at several prestigious national meetings including the American Society for Clinical Investigation/American Association of Physicians in April 2012 (poster), the 26th Annual Keystone MD/PhD Conference in July 2011 (poster), and the Southeast Medical Scientist Symposium in September 2011 (poster). David was also encouraged to present his thesis work at two internal Research Days at UAB. He was awarded the "Best Poster" award in the Immunology category at the UAB Medical Student Research Day, October 2011, and won 1st place for his oral presentation at the UAB Graduate Student Research Day, February 2012. David has participated in Brain Tumor Board, is taking the weekly Cancer Biology Journal Club, attends the weekly Cell Biology Seminar Series, and attends the Comparative Medicine Seminar as part of the MSTP Program. David is starting to publish his thesis work, and is currently first author on a review article in *Future Virology* (2011).

Postdoctoral (**Braden McFarland, Ph.D.**). Dr. McFarland joined Dr. Benveniste's laboratory in 2009 for her postdoctoral studies following completion of her PhD in Neurosciences with Dr. Candece Gladson. Her postdoctoral research is focused on studies in mouse models of GBMs to investigate the involvement of the JAK/STAT and NF-κB pathways in tumor progression. She demonstrated that pharmacologic inhibitors of the JAK/STAT pathway increase survival of mice with intracranial tumors by inhibiting STAT3 activation. In 2009, she was recruited as a postdoctoral trainee on the "Rheumatic Diseases Research" T32 training grant due to the immunologic aspects of her work, and in July 2011 was appointed as a postdoctoral trainee on this training grant. Dr. McFarland's studies have led to productive collaborations with other investigators associated with this T32 grant, including Drs. Burt Nabors, Yancey Gillespie, Chris Willey and Markus Bredel. One first-author publication has resulted from her work (*Molecular Cancer Therapeutics*, 2011), with two additional first-author publications in preparation. While a trainee on this training grant, Dr. McFarland was successful in obtaining her own individual American Brain Tumor Association Postdoctoral Fellowship in 2012, and has a NIH K99/ROO Award pending review in June 2012. Dr. McFarland took advantage of the enrichment activities associated with the training grant including the OPE Course on Grant Writing, presenting at the CCC Annual Retreat (1st place award in 2009), and at UAB Postdoctoral Research Day, winning 1st place in 2010 and 2nd place in 2011. The impetus for the newly proposed TCGA/Bioinformatics Tutorial came from work Braden did with Dr. Markus Bredel to investigate STAT3 gene alterations in GBMs, and representation in the four molecular subtypes. This interaction, and the subsequent data generated, was invaluable for the formulation of her ABTA and NIH grant applications.

3E. Training Program Evaluation

At the beginning of the research training period, mentors and trainees develop a written set of activities and goals including didactic courses, ongoing conferences and seminars, and the mentored research project. These goals provide the framework for periodic assessment of progress in the training relationship and are reviewed at least annually with the Program Directors and the Executive Committee. The Annual Progress Report (**APPENDIX G)** provided by the trainees/mentors will hold all accountable for progress each year, and alert the Directors of problems that need to be addressed. Feedback from trainees during the past funding period have included the following: "The mock grant writing/study section was extremely beneficial"; "The progress reports helped me to evaluate my work and stay on track"; and "The Advanced Course in Brain Tumor Biology was one of the best classes I have had in graduate school".

Over the longer term, the overall program is evaluated using the outcomes reflected in the percent of trainees remaining in research and academic medicine, and in the number of trainees pursuing interdisciplinary research related to brain tumor biology. For example, over the last five years, 8 postdoctoral and 6 predoctoral trainees have been supported, with 13 of 14 continuing in academic biomedical research, teaching, further research training and/or medical school. The single predoctoral trainee who left graduate school and the training program came to the conclusion that he did not have the necessary passion and commitment to be successful in this field. **Our trainees in this five year period have been 57% male and 43% female; and have included 22% under-represented minorities (African American and Hispanic American).**

3F. Trainee Candidates: Recruitment, Qualifications and Selection

The current and past training record of the Program Faculty is presented in **TABLES 5A and 5B**. Applications, qualifications, recruitment, assignments and completion records for this training program are presented in **TABLES 7A, 7B, 8A, 8B and 10**.

Applicant Recruitment and Selection.

1. Predoctoral students are drawn from the graduate thematic programs in GBS and in the MSTP. Applications for students in the laboratories/research settings of Program Faculty are solicited from all Program Faculty and reviewed for programmatic relevance, for performance in the core curriculum and for assessment of potential by the mentor. The Executive Committee reviews each appointment. Recognizing the opportunity to enhance recruitment to brain tumor research, the faculty mentors have developed new thematically oriented graduate courses and journal clubs embracing translational research. **It should be noted that there are currently 17 TGE predoctoral trainees working in the laboratories of the Program Faculty that could be immediately placed on this training grant during the next funding cycle, and easily fill the 3 requested positions.** This documents an existing pool of qualified graduate students working in the area of brain tumor biology.

2. Postdoctoral trainees are recruited by several complementary mechanisms: 1) the Office of Postdoctoral Education maintains an active web site, complementing the School of Medicine's research portalhttp://www.uab.edu/uasom/research/ and a listing of positions. These sites are designed to make potential postdoctoral fellows aware of the resources available at UAB and to facilitate fellow-initiated contacts. 2) The more traditional recruitment of postdoctoral fellows is investigator-driven and based on networking amongst colleagues and contacts at scientific meetings. Applications for available positions, consisting of biosketches, recommendations of the thesis mentor and the postdoctoral mentor, a preliminary outline of the proposed training plan and an interview with at least two members of the Executive Committee, are reviewed and assessed by the Executive Committee. Selections are made on the basis of the candidate's potential to develop as an independent investigator as judged by publications and the mentors' evaluations.

3. Residents. The national prominence of the residency programs at UAB ensures a pool of high quality trainees. These residents are already at UAB, and will be recruited for this T32 grant by individual faculty who recruit independently into their own research programs. Contributing residency programs include Neurosurgery, Neurology, Radiation Oncology and Neuropathology. The participating residency programs have a total **annual** pool of **15** resident candidates; 3 from Neurosurgery, 6 from Neurology, 5 from Radiation Oncology and 1 from Neuropathology. One of the previous trainees (Dr. D. Bauer) was from our Neurosurgery residency, where residents are encouraged to take two years in research training in preparation for academic careers. Dr. Bauer has accepted an Assistant Professor position at Dartmouth, effective July 2012.

The combined number of TGE postdoctoral trainees and residents ensure that the requested 3 positions in the competitive renewal will be readily filled.

3G. Institutional Environment and Commitment to Training

The University, School of Medicine, and the Graduate School have provided substantial support for the development of a research training infrastructure as exemplified in the new GBS programs (**APPENDIX A1-A6**), in the Office of Postdoctoral Education (**APPENDIX B**), the Medical Scientist Training Program (**APPENDIX A8**), and the UAB Howard Hughes Medical Institute (HHMI) MED-GRAD Fellowship (HMGF) (**APPENDIX A9**). Each of these efforts provides complementary support for research career development.

The SOM and the CCC have made a tremendous commitment to the Neuro-Oncology Program at UAB by performing a $35 million renovation of research laboratories in the Wallace Tumor Institute. Ten of the 26 faculty members of the Neuro-Oncology Program in the Comprehensive Cancer Center relocated their labs and offices to the 7th floor of the newly renovated Wallace Tumor Institute in April 2012. The floor has 10 faculty offices, a fellows' suite, a conference room, and an open break area located in the center of the building around an open atrium. This design concept has resulted in new collaborations and numerous new interactions. **Drs. Roth, Gillespie, Nabors and Griguer are in the new space, and there is additional lab space for new recruits in Neuro-Oncology**. The 6th floor has a 10,000 ft^2 fully equipped (Opti-Mouse/Opti-Rat racks, biosafety hoods, Kimtron 320KV xray machine, cage wash, storage), self-contained Animal Research Facility to support rodent-based research with a capacity for over 7,500 fully ventilated cages (>37,000 mice).