



*Perspectives in Research* is a series of articles written by David R. Hurwitz, PhD. Dr. Hurwitz holds the Richard B. Ross Chair and is NBTS' Chief Scientific Officer. These articles are the culmination of thoughts and analyses on key issues related to brain tumor research.

## NBTS to Embrace Systems Biology Approach to Brain Tumor Research

*The multiple biological complexities have led NBTS to a systems approach.*

By David R. Hurwitz, PhD

**Brain tumor research, particularly relating to glioblastoma (GBM),** has yielded much data in recent years, and one of the most valuable conclusions from new information is that all GBMs are not the same. Different subtypes of GBM exhibit different combinations of genomic/molecular/expressional alterations. Furthermore, different subtypes of GBM produce different responses to aggressive chemotherapy and radiation treatment.

Because there are so many levels of complexities to understanding GBMs, the National Brain Tumor Society is embracing a systems biology approach. Systems biology focuses research on biological systems as a whole, rather than pursuing the traditional avenue of considering individual genes, proteins, parts of an organism, or interaction of a limited number of these.

Given that brain tumors are dynamic systems whose complexity results from the interaction of biochemical, molecular, and cellular processes that change over time, NBTS feels that it must embrace a systems approach. We are optimistic this will have a positive impact, benefiting patients, families, doctors, researchers, and health professionals.

### Classifying Brain Tumors

The World Health Organization has classified more than 120 tumors and tumor variants of the brain and central nervous system based on histopathologic criteria. This includes more than 50 types and variants of primary brain tumors that are derived from brain tissue itself. Different brain tumor types may predominate in adults (20 year old +) or in children (1-19 years old). Tumors can be malignant and grow rapidly or they might be non-malignant, though slow growing non-malignant tumors can be extremely dangerous over time to those who are diagnosed. Furthermore, primary brain tumors can reside throughout all regions of the brain. The

growth of different tumor types is driven by different patterns of aberrant molecular biologies.

In itself, the range of brain tumor types and their different growth, distribution, and molecular characteristics makes the field of brain tumor research and brain tumor therapy highly complex. But this level of complexity is only the beginning of the story. Specific tumor types (based on their histopathology) and individual tumors exhibit enormous cellular, biochemical, and molecular complexities that make the discovery and development of effective therapies for even a single tumor type extremely challenging.

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Of all cancers, GBM is perhaps the most comprehensively analyzed in terms of genomic, epigenomic, and gene expressional alterations. This is the result of the collective work of independent researchers as well as of the collaboration by the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) through The Cancer Genome Atlas (TCGA) program, and the collaborative work of The Johns Hopkins Kimmel Cancer Center and Duke University.

These studies, combined with the work by other dedicated and talented laboratory and clinical researchers, have illuminated the enormous complexity involved in brain tumor biology and the challenges in developing effective therapies.

#### **Brain tumor biological complexity manifests in a number of ways:**

- The heterogeneity of tumors from one patient to the next. Different GBMs fall into different subtypes that reflect different sets of gene and expression alteration patterns. An interventional therapeutic approach for a GBM of one subtype would not necessarily work on a GBM of another subtype. In fact, earlier this year a group from the University of North Carolina at Chapel Hill demonstrated that different GBM subgroups respond differently to chemotherapy and radiotherapy.
- The complexity, interconnections (cross talk), redundancies, feedback loops, and multiple mutations within the signaling/biochemical pathways that drive the growth of tumors. This level of complexity allows tumors to find ways around the inhibition of particular components of offending pathways.
- The heterogeneity of cells that make up and drive the growth of individual brain tumors, including brain tumor stem cells, progenitor cells, and mature tumor cells.
- The high rate of mutations within tumors that allows for the growth of different cell populations that possess different sets of gene and expression alteration patterns within individual tumors.
- Phenotypic plasticity of tumor cells, where tumor cells exhibit changes in their biological characteristics in response to changes in their microenvironment, in the absence of genomic changes. This plasticity potentially makes tumor cells moving targets for therapies.

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These layers of biological complexity involved in the growth and recurrence of brain tumors account for the fact that GBMs recur despite traditional chemotherapy and radiotherapy and that thus far, GBM clinical trials that target individual molecular targets have been unsuccessful. Furthermore, while it is generally accepted that combination therapies will have a better chance of success than monotherapies, it is not clear which combinations of targets would be best to attack.

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#### **Systems Biology**

Systems biology is the study of complex biological problems as integrated and interacting networks of their components, which is used to understand higher-level properties of complex biological systems such as tumors. Systems biology focuses research on biological systems as a whole, rather than pursuing the traditional approach of considering individual genes, proteins, parts of an organism, or the interaction of a limited number of these.

The potential power of systems biology research is exemplified by the report issued in December 2009 by the SCImago Research Group on the evaluation of the impact of scientific research publications (2003 to 2007) from over 2,000 research institutions around the world. Scientific publications from the Institute for Systems Biology (ISB), an independent research institute in Seattle, were deemed to have the highest scientific impact in the United States and the third highest scientific impact worldwide. Its average scientific impact score was greater than twice the average impact score for all institutions in the world. Only three other institutions worldwide had

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an average impact at the level of twice or greater than the global impact.

The concept of systems biology is being embraced by many universities that have established systems biology departments and programs. The National Human Genome Research Institute (part of The National Institutes of Health) currently funds 10 National Centers for Systems Biology. Independent research institutions such as the ISB are focused on systems biology research and have developed their institutional structures and programs in order to optimize the facilitation of the multi-disciplinary nature of systems biology research.

Conferences on systems biology have also been on the rise. In May 2010 the Massachusetts General Hospital, in collaboration with Sweden's Karolinska Institutet, will convene an international conference in Stockholm entitled "Days of Molecular Medicine 2010: Systems Biology Approaches to Cancer and Metabolic Disease." Recognizing that cancer is a complex multi-factorial disease, the conference will focus on "the application of systems biology to studying cancer and diabetes, and to developing therapeutics and strategies to combat them."

### Systems Biology and Brain Tumors

Systems biology is often referred to as a field at the intersection of biology, applied mathematics, engineering, and the physical sciences. The comprehensive genomic/molecular profiling of GBMs by many researchers, including the Cancer Genome Atlas program, reflects this intersection. The collaboration among researchers at UCLA, Caltech, and ISB on characterizing the individual cells of individual brain tumors using nanotechnology and microfluidics also exemplifies this situation.

Brain tumors are dynamic, complex systems whose complexity as described above results from the interaction of different sets of macromolecules, metabolites, biochemical pathways and networks, multiple cells that vary in their genomic/epigenomic/phenotypic characteristics, microenvironments, and interactions with their microenvironments. However, all of this may change over time and in response and adaptation to environmental assaults such as therapeutic agents.

Innovative approaches to understand the dynamic complexity of brain tumors could promote conceptual insights and practical innovations that have major implications in the development of new therapeutic approaches and transform the lives of many individuals with brain tumors. We believe in the potential impact of research that focuses on the interactions among individual elements of a complex biological system that characterizes brain tumors and that epitomizes the need for a systems biology research approach.

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Dr. Hurwitz is the Richard B. Ross Chief Scientific Officer of the National Brain Tumor Society. He has an academic background in genetics and molecular virology and has been a lead scientist in industry laboratories and companies. He has authored peer-reviewed research publications in the areas of viral oncogenesis, signal transduction and tyrosine kinase receptors, gene therapy, and transgenics, and is an inventor on 6 issued biotechnology patents. At the NBTS, Dr. Hurwitz leads the research program, collaborating with prominent experts across the US, and is charged with the NBTS strategic research plan and its implementation.

### About National Brain Tumor Society

Today there are over 600,000 people in the US living with the devastating diagnosis of a brain tumor and NBTS is fiercely committed to improving the lives of all those affected. Learn more about our comprehensive patient, family, and caregiver services, our targeted adult and pediatric brain tumor research programs, and our latest advocacy efforts at [www.braintumor.org](http://www.braintumor.org).



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