Molecular neurooncology

Primary brain tumors are heterogeneous in histology, genetics, and outcome. Although World Health Organization Classification of Tumors of the Central Nervous System has greatly helped to standardise diagnostic criteria worldwide, it does not consider the substantial progress that has been made in the molecular classification of many brain tumours.

Molecular neurooncology has begun to clarify the transformed phenotype of brain tumors and identify oncogenic pathways that might be amenable to targeted therapy. Activity of the Phosphoinositide 3 kinase (PI3K)/Akt pathway is often upregulated in brain tumors due to excessive stimulation by growth factor receptors and Ras. Loss of function of the tumor suppressor gene PTEN also frequently contributes to upregulation of PI3K/Akt. Several compounds, such as wortmannin and LY-294002, can target PI3K and inhibit activity of this pathway. The mammalian target of rapamycin (mTOR) is an important regulator of cell growth and metabolism and is often upregulated by Akt. Clinical trials of CCI-779, an inhibitor of mTOR, are ongoing in recurrent malignant glioma patients. The sonic hedgehog/PTCH pathway is involved in the tumorigenesis of some familial and sporadic medulloblastomas. This pathway can be targeted by cyclopamine, which is under evaluation in preclinical studies. Angiogenesis is a critical process for development and progression of brain tumors. Targeted approaches to inhibit angiogenesis include monoclonal antibodies, receptor tyrosine kinase inhibitors, antisense oligonucleotides and gene therapy. Clinical trials are ongoing for numerous angiogenesis inhibitors, including thalidomide, CC-5103 and PTK 787/ZK 222584. Further development of targeted therapies and evaluation of these new agents in clinical trials will be needed to improve survival and quality of life of patients with brain tumors [1)].

Clinical trials have defined a role for routine assessment of MGMT promoter methylation in glioblastomas in elderly people, and 1p19q codeletions in anaplastic oligodendroglioma. Moreover, large-scale molecular profiling approaches have identified new mutations in gliomas, affecting IDH1, IDH2, H3F3, ATRX, and CIC, which has allowed subclassification of gliomas into distinct molecular subgroups with characteristic features of age, localisation, and outcome. However, these molecular approaches cannot yet predict patients' benefit from therapeutic interventions. Similarly, transcriptomics-based classification of medulloblastoma has delineated four variants that might now be candidate diseases in which to explore novel targeted agents [2)].

Books

Genomic and Molecular Neuro-Oncology.

Edited by Wei Zhang and Gregory N. Fuller, is an up-to-date reference that documents these important advances and describes their medical and therapeutic implications. Written for a broad range of researchers and clinicians including oncologists, neurologists, pathologists, neuroscientists, residents, postdoctoral fellows, and others in related fields, this volume contains 18 contributions organized in five sections: Genomic and Genetic Alterations in Gliomas, Molecular Alterations in Gliomas, Genomics and Informatics, Animal Models, and Molecular Therapeutics. Each chapter provides a review of a specific subfield of contemporary molecular neuro-oncology, including recently implemented diagnostic and research applications. This book focuses on the latest genomics,

molecular, and informatic approaches to neuro-oncology. The broad range of applications illustrated include the facilitation of clinical diagnosis through molecular and genomics techniques, the identification, confirmation and validation of new tumor markers and novel therapeutic targets, gene discovery and subsequent pathway and biology elucidation, and the emerging molecular approach to brain tumor classification. There is a naturally symbiotic relationship between advances in basic knowledge generated through bench research and the clinical translation and application of that knowledge that forms the foundation for each of the chapters in Genomic and Molecular Neuro-Oncology.

Features & Benefits The first book that highlights the latest genomic, molecular approaches, and informatics applied to human brain tumor classification and target identification.

Contains a comprehensive review on genomic instabilities, mRNA splicing, key signal transduction pathways, and tumor suppressor genes important for neuro-oncology.

Includes a thorough review of animal models, especially recently developed glial-specific transgenic models, used in contemporary neuro-oncology research.

Thoroughly documents the translation of modern neuro-oncology research to clinical therapeutics.

Applicable Courses The target audience for Genomic and Molecular Neuro-Oncology is broad and includes clinicians, neuroscientists, graduate students, medical residents, and postdoctoral fellows working in the field of neuro-oncology and related disciplines. Because of the focus on very timely, state-of-the-art genomics approaches, the book will also be of interest to genomics researchers, molecular biologists, bioinformaticians and statisticians in all fields of biological and biomedical research. This book is appropriate for all institutions that have cancer biology-related educational programs at college and graduate school levels and can be used as the core or main text for Neuro-oncology courses and as a supplementary book for all other cancer biology-related courses.

1)
Newton HB. Molecular neuro-oncology and development of targeted therapeutic strategies for brain tumors. Part 2: PI3K/Akt/PTEN, mTOR, SHH/PTCH and angiogenesis. Expert Rev Anticancer Ther. 2004 Feb;4(1):105-28. Review. PubMed PMID: 14748662.
2)
Weller M, Pfister SM, Wick W, Hegi ME, Reifenberger G, Stupp R. Molecular neuro-oncology in clinical practice: a new horizon. Lancet Oncol. 2013 Aug;14(9):e370-9. doi: 10.1016/S1470-2045(13)70168-2. Review. Erratum in: Lancet Oncol. 2015 May;16(5):e199. PubMed PMID: 23896276.