

PROGRESS IN CLINICAL
AND BIOLOGICAL RESEARCH
VOLUME 366

**ADVANCES IN
NEUROBLASTOMA
RESEARCH 3**

Editors: Audrey E. Evans
Guilio J. D'Angio
Alfred G. Knudson, Jr.
Robert C. Seeger

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ADVANCES IN NEUROBLASTOMA RESEARCH 3

Proceedings of the Fifth Symposium on Advances in Neuroblastoma
Research, Held in Philadelphia, Pennsylvania, May 28–30, 1990

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NEW YORK • CHICHESTER • BRISBANE • TORONTO • SINGAPORE

Publisher
New York, NY 10003

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Preface

This volume records the proceedings of the Fifth Symposium on Neuroblastoma Research, held at The Children's Hospital of Philadelphia in May 1990. The variety and scope of the research in this field has expanded enormously since the first neuroblastoma symposium in 1975. This is reflected in the content of the 120 abstracts submitted for presentation. Many of them dealt with molecular genetics and biology. The discussions in the clinical area now go well beyond modifications of standard chemotherapy regimens. The topics now addressed include the use of biological response modifiers, "targeted therapy" with MIBG, and "megadose" chemotherapy with marrow rescue.

The initial session dealt with N-myc amplification, its control, and expression. This oncogene has been studied in great detail since the associations between N-myc amplification, more advanced stages of neuroblastoma, and a poor prognosis were described. The research now is focused on N-myc expression and control, and the associated genetic abnormalities. At this meeting, there were reports on the effect of antisense, ubiquitin, and iron on N-myc expression, as well as a discussion of the prolongation of N-myc protein half life in a cell line without gene amplification. Another study, involving the association between 1p deletion and N-myc amplification (both associated with high-risk neuroblastoma), concluded that the molecular mechanisms involved in these two abnormalities are not directly linked. Five papers on cytogenetics relate ploidy index to prognosis, and another reports loss of heterozygosity for alleles on chromosomes 11q and 14q. The finding of triploidy and its significance in the majority of tumors detected in infants by mass screening was discussed at length following the presentations on screening.

Several sessions were devoted to differentiation, the first one dealing with retinoic acid. The effect of retinoic acid on cell growth was addressed by several investigators, and one group reported that it increased the expression of insulin-like growth factor receptors.

Others reported that the constitutive expression of N-myc does not block retinoic acid-induced growth arrest and that resistant human neuroblastoma cells containing the multiple drug resistance gene MDR, already more differentiated than controls, can be further differentiated by retinoic acid. One paper reported clinical benefit from the use of retinoic acid—it caused disappearance of tumor cells in marrow in two of three patients with recurrent disease.

There was a half-day session dealing with growth factors and their receptors. One discussed the multiple defects in the nerve growth factor receptor pathway in various neuroblastoma cell lines, and the second showed the varying amount of NGF receptors on neuroblastoma, peripheral neuro-epitheliomas (PNET), and CNS PNETs. Another paper reported the transfection with the NGF receptor gene causing terminal differentiation in neuroblastoma cells when treated with NGF. Expression of other molecules included polysialic acid, tissue-specific N-CAMS, and differential lineage-specific gene expression. High plasma levels of neuropeptide Y (NPY) are associated with a poor prognosis. The paper by Dr. Osama El Badry, selected for the Andrew Seligson Memorial Lecture, dealt with insulin-like growth factor II (IGFII). Dr. El Badry had noted that cells grown in serum-free medium secreted GF-II and postulated that this acted like an autocrine/paracrine growth factor. In examining tissue sections, he noted increasing amounts of IGF-II in the more aggressive tumors and an infiltration of eosinophils in those tumors without IGF-II. Dr. El Badry speculates that eosinophils rich in IGF-II provide a source of IGF-II not found in the tumor.

Two of the papers devoted to therapy discussed the effects of monoclonal antibody, 3F8, when used alone, radiolabeled, and given together with monocytes activated with human macrophage colony-stimulating factor. Other biological modifiers addressed were gamma-interferon, interleukin II, LAK, and TIL cells used for therapy. There was a half-day session dealing with I-131- and I-125-labeled MIBG, its metabolism, biodistribution, and microdosimetry. The chemotherapy discussion included three on high-dose chemotherapy followed by bone marrow transplantation, two discussing the effects of carboplatin, and another reporting a large review of dose intensity and therapeutic effectiveness.

The meeting ended with four papers on the screening of infants for early detection of neuroblastoma. This was followed by a brisk discussion on the value of this technique. Questions were raised as to the implications of detecting infants early in life with low-stage disease. Were these children who would have developed more advanced dis-

ression of N-myc does not and that resistant human multiple drug resistance gene controls, can be further differed clinical benefit from the use of tumor cells in marrow disease.

th growth factors and their effects in the nerve growth neuroblastoma cell lines, and the TrkA receptors on neuroblastoma (T), and CNS PNETs. Although the NGF receptor gene neuroblastoma cells when treated with sialic acid, stage-specific gene expression (NPY) are associated with El Badry, selected for the role with insulin-like growth that cells grown in serum showed that this acted like an inhibiting tissue sections, he more aggressive tumors and tumors without IGF-II. Dr. El IGF-II provide a source of

discussed the effects of the, radiolabeled, and given human macrophage colony-forming units addressed were gamma-rays used for therapy. There and I-125-labeled MIBG, its scintigraphy. The chemotherapy chemotherapy followed by studying the effects of carboplatin dose intensity and thera-

the screening of infants for followed by a brisk discussions were raised as to the role with low-stage disease. developed more advanced dis-

ease later? Or were they those in whom the disease would have regressed spontaneously and never developed clinical evidence of neuroblastoma? The issue remains unresolved.

This volume will be of value not only to basic scientists and clinicians interested in neuroblastoma but also to those studying the basic mechanisms of malignant transformation and their control.

Audrey E. Evans