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Foreword

NEUROBLASTOMA IS one of the most fascinating and challenging of paediatric neoplasms. In some patients, especially infants, the tumour may develop and even metastasise, only to regress spontaneously. In other patients, particularly older children, the tumour may differentiate into a benign ganglioneuroma. Unfortunately, the majority of children diagnosed with neuroblastoma are over a year of age with widespread metastatic disease and their outcome is poor. Despite very intensive chemotherapy supported with autologous bone marrow or stem cell rescue, 5-year survival for these patients is probably only 20–25%, so clearly more effective and less toxic therapy is needed. To accomplish this, greater understanding of the genes, proteins and pathways responsible for malignant transformation and progression may be necessary.

A meeting entitled: 'Advances in Neuroblastoma Research—1996' was held in Philadelphia, Pennsylvania, U.S.A. on 22–25 May 1996 to discuss the current state of basic and clinical research in neuroblastoma. This was the 7th in a series of meetings held in Philadelphia since 1975, generally at 3–4 year intervals. At least two similar meetings have been organised in Heidelberg, Germany between the last three Philadelphia meetings. At the second of these, it was decided to hold the Advances in Neuroblastoma Research meetings every 2 years, alternating between Philadelphia and somewhere outside the U.S. The next meeting entitled Advances in Neuroblastoma Research—1998 will be held in Bath, U.K. on 15–17 June 1998. This special issue of the *European Journal of Cancer* contains manuscripts and abstracts summarising the reports presented at the 1996 meeting.

Despite the limited progress in curing advanced stage neuroblastomas, a great deal of progress has been made in understanding this disease from a genetic and biological perspective. The oncogene *MYC*N has been shown to be amplified in approximately 20% of neuroblastomas and this feature is strongly correlated with advanced stages of disease and a poor outcome. Genes that regulate *MYC*N expression and function may also be important. Interestingly, there was a report of a transgenic mouse that had targeted overexpression of *MYC*N in sympathetic neurons and developed neuroblastomas with substantial frequency (see Weiss and associates, Abstract—p. 2137). This animal model may be useful in studying the molecular pathogenesis of neuroblastoma.

Although no specific tumour suppressor genes have been shown to be mutated or inactivated, consistent deletion or allelic loss has been demonstrated at several chromosomal sites. Deletion of the distal short arm of chromosome 1 (1p) has been the most intensively studied and current evidence suggests there may be more than one tumour suppressor gene in this region. Several potential candidate genes mapping to this region have been analysed, including *HKR3* and *DAN*. Other sites of consistent deletion are 11q and 14q and newer sites have been suggested at 3p, 4p and 18q. Gain of sequences on 17q and 1q have been associated with more aggressive tumours.

Work was presented regarding familial neuroblastomas and attempts to localise the predisposition gene by linkage analysis in families (see Maris and associates, pp. 1923–1928; Tonini and associates, pp. 1953–1956). Despite reasons to suspect that the predisposition gene might map to distal 1p, linkage was not found. Also, there was no evidence of linkage to several other genetic loci that are frequently deleted in sporadic neuroblastomas, or that contained potential candidate genes.

Another area of considerable interest are the ligand-receptor pathways that may be involved in the survival or differentiation of immature neuroblasts. The neurotrophin nerve growth factor binds to the transmembrane tyrosine kinase receptor trk-A and promotes survival of normal sympathetic neurons. Trk-A expression is also seen in a substantial number of primary neuroblastomas and high expression is associated with lower age, lower stage and a favourable outcome. Also, Trk-A expression is inversely correlated with *MYC*N amplification. A homologous pathway involves the ligand brain-derived neurotrophic factor and its cognate receptor, Trk-B, particularly those with *MYC*N amplification. This appears to be an autocrine survival pathway for a subset of aggressive neuroblastomas. The importance of the neurotrophin-3/trk-C pathway is still under investigation, but trk-C is expressed primarily in tumours with high trk-A expression.

Retinoid compounds also have been shown to induce morphological and biochemical differentiation in neuroblastoma cells in culture. Although the precise role of retinoids and their receptors in physiological differentiation of sympathetic neuroblasts is unclear, certain retinoid compounds (13-cis retinoic acid, 9-cis retinoic acid, fenretinide) are under investigation as a form of therapy for patients with minimal residual disease. There was an interesting report of identification of a 260 kD antigen which is the target of a naturally occurring IgM that may be involved in spontaneous regression of neuroblastomas (see David and associates, pp. 1937–1941; Ollert and associates, pp. 1942–1948). Furthermore, the antigen may be an attractive target for immunotherapy.

A number of genetic changes and patterns of expression have been identified that correlate with prognosis. A poor prognosis has been associated with *MYC*N amplification and overexpression, 1p LOH, 17q trisomy, *MDR1* expression, MRP expression, and telomerase activity. A favourable outcome is associated with expression of trk-A, CD44, somatostatin receptors, and ICE. The biological significance and involvement in pathogenesis or progression of each of these genes or genetic loci was discussed.

An international consensus has been reached on the definition of biological risk groups for neuroblastoma (INRG) that may permit the intensity of therapy to be based on the individual features of a patient's tumour (see Castleberry and associates, pp. 2113–2116). Results of a mass screening effort in Quebec, Canada suggest that screening for neuroblastoma at 3 weeks and 6 months of age doubles the apparent prevalence of the disease, but has no impact in the prevalence or stage distribution of neuroblastoma in patients over 1 year of age (see Woods and associates, pp. 2106–2112). There were several reports of chemotherapy protocols combined with myeloablative therapy and marrow/stem cell rescue that offer promise of improved outcome. Finally, there were several reports of novel agents (betulinic acid, angiostatic agents), drug combinations (buthionine sulphoximine and melphalan) and targets (topoisomerase I) for therapy.

Although considerable progress has been made since the last neuroblastoma meeting, (see the *European Journal of Cancer*, **31A**, Issue 4, 1995) there is still much to be learned. However, there is promise that further elucidation of the molecular and biochemical mechanisms underlying malignant transformation and progression of neuroblastomas will ultimately lead to novel approaches that will be more e**ff**ective and less toxic than current therapy.

We are extremely grateful to all who contributed to making this meeting a success. We are particularly indebted to Ms. Deborah Marlowe, whose tireless efforts and subtle touches helped make this such a successful and enjoyable meeting. In closing, the organisers and investigators at the meeting were delighted and honoured to present Dr Audrey E. Evans with a Lifetime Achievement Award. Her efforts over the past 25 years to the biological understanding, clinical staging and treatment (or observation) of children with neuroblastoma have been an inspiration to us all.

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