Eur J Cancer Clin Oncol, Vol. 24, No. 2, pp. 283–284, 1988.
Printed in Great Britain

0277-5379/88$3.00+0.00

News from EORTC

New Concepts in Anticancer Drug Design

B.W. Fox (on behalf of the Screening and Pharmacology Group
Paterson Institute for Cancer Research, Christie Hospital, Wilmslow Road, Withington, Manchester M20 9BX, U.K.

Workshop held at the Radiobiological Institute TNO, Rijswijk, The Netherlands, 11–12 December 1986

THE PRIME aim of this workshop, organized by the Screening and Pharmacology Group of the EORTC, was to enable senior chemists from a number of different European Groups to get together and discuss ideas involved in the design of new drugs for the treatment of cancer. It enabled organic synthetic chemists to discuss chemical problems in the synthetic methods used as well as to exchange ideas on further new drug development.

After general welcoming introductions by Dr Peter Lelieveld (Secretary, SPG) and Professor D.N. Reinhoudt (Workshop chairman), Professor B.W. Fox outlined the ideas of receptor mapping of possible bifunctional nucleophilic centres that require to be attacked in order to result in anti-tumour activity as opposed to those which result in toxicity effects, to normal tissue systems such as haemopoeisis, the gastrointestinal tract, etc.

The talk was illustrated with a description of some of the work that has been conducted amongst the dimethanesulphonate esters, showing that there appears to be a fairly clearly defined three-dimensional geometry required by the alkylating groups to produce antitumour activity, which may not be the same that is required to produce toxicity.

Dr F. Arcamone (Farmitalia) described some new chemical approaches to the development of anticancer drugs in the anthracycline field. He outlined some new modifications of the typical anthracycline structures in both the aglycone and the carbohydrate moieties. He concluded that these changes brought about DNA base preference changes during intercalation. Assay of these types of drugs thus requires the development of new systems which have specific base requirements for their expression. From this work, he described some of the remarkably selective actions of distamycin analogues, seen even at the level of chromosome breakages. Some new irreversible aromatase inhibitors as well as dopamine antagonists were also described.

Professor David Reinhoudt (Twente University, The Netherlands) discussed some of the work of his group on novel bioreductive agents in the mitosene group. The concept of bioreductive activation is potentially of major significance as a mechanism of action of many naturally occurring and synthetic antineoplastic compounds. In most cases they rely on the formation of reduced quinone compounds with considerably enhanced activity following reduction of a quinone moiety *in vivo*. The mitosenes are a particular group of these agents based on the structure of mitomycin C.

Dr S. McElhinney has been developing a series of fluorouracil analogues in which the principle of producing molecular combinations of anticancer drugs has been exploited. The principle is well known for the analogues of fluorouracil in which slow release of the agent is required, such as in the tetrahydrofuran derivative Ftorafur. In this case a series of chloroethylnitrosourea derivatives has been prepared and several analogues of this series have already been shown selective activity in a series of colon tumours studied by Dr John Double (Bradford, U.K.).

Professor Malcolm Stevens (University of Aston, U.K.) described the exploitation of the aromatic azido group as an anticancer agent, especially in reference to the development of some new lipophylic anticancer folates, producing new dihydrofolate reductase inhibitors. One of the best of these, the ethane sulphonic acid salt of 2,4-diamino-5-(3-

Accepted 5 August 1987.

azido-4-chlorophenyl)-6-ethylpyrimidine (MZPES) is a very important inhibitor of rat liver dihydrofolate reductase and is presently undergoing clinical trials in the U.K.

The development of sparsomycin, a fungal metabolite, was described in detail by Dr H.C.J. Ottenheijm (University of Nijmegen). This agent possesses the unusual monooxodithioacetal grouping as an active function of the molecule. Following a successful total synthesis of the antibiotic, new analogues with increased lipophylicity have now been prepared and two of these are due to be considered as candidates for clinical trial.

An exciting new development in the field of drug design was described by Professor C. Paoletti (Institut Gustave Roussy, France). Protooncogene activation has been implicated as involved in the induction, maintenance and progression of human malignant phenotypes. Some of these are substantially amplified in several human tumours and the possibilities of controlling the expression at the mRNA level has now been seriously exploited. The description of the development of antisense RNA, designed to exert a negative action on the RNA expression of oncogenes was carefully reviewed, especially in relation to the possible multigenic character of the malignant expression. A series of tetrathymidylates were described which were designed to interact covalently with the DNA intercalator head. The results described, including electropermeabilization techniques, opened the way to some applications of such oligonucleotides as antisense ligands to the transcription products of some oncogenes, and heralds an exciting new area of potential anticancer drug therapy.

Dr D.E.V. Wilman (Royal Marsden, London) then outlined the rationale behind the development of a second generation triazene as a successor to DTIC. The agent selected from a wide group of agents tested (CB 10–277) is better activated by the rat than the mouse and cytotoxic levels of the agent are achieved in each species. It was clear from this work that the activity within this group of agents was very dependent on the host capacity to activate the molecule. CB 10–277 is currently undergoing clinical trial in the U.K.

Finally, Professor G. Eisenbrand described a series of new receptor-affine antineoplastic agents and discussed new developments in the design and synthesis of chloroethylnitrosourea derivatives of short chain peptides as well as important steroids such as estradiol. It was clear from this work that hormones could be used principally as carriers to important regulatory sites, without necessarily exerting hormonal activity.

The meeting was felt to be a considerable success and allowed organic synthetic chemists within the EORTC and experts from outside to get together and discuss detailed problems of mutual interest to this important group of scientists at the root of new anticancer drug development.