FRIDAY
AUGUST 28, 1987

ABSTRACTS

XTH INTERNATIONAL CONGRESS OF PHARMACOLOGY
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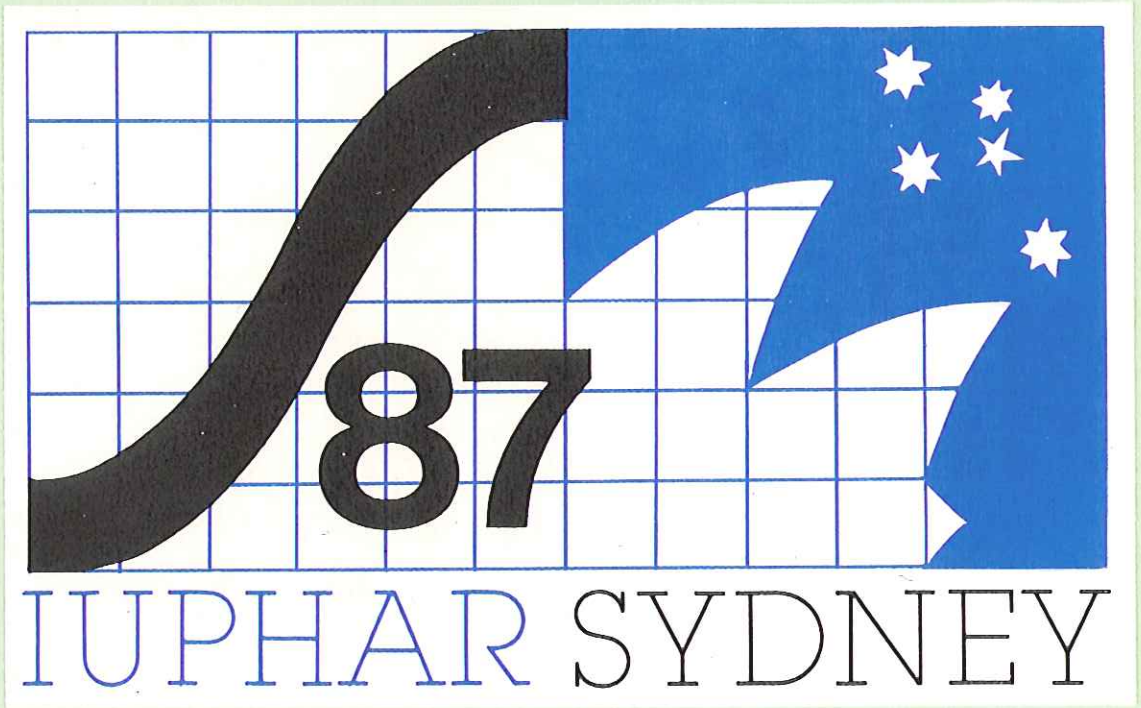

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Antineoplastons

Friday, August 28, 1987
16.00-17.30
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THE CRYSTAL AND MOLECULAR STRUCTURE OF *ANTINEOPLASTON A10*

D.J. Williams, Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, U.K.

The crystal and molecular structure of the anti-tumor agent *Antineoplaston A10* (1) has been determined by single crystal *X*-ray diffraction. The compound $C_{13}H_{14}N_2O_3$ crystallises from toluene as very thin interpenetrating fibrous plates. The crystals are orthorhombic, a = 5.993(3), b = 9.561(5), c = 42.487(29)Å, space-group $Pbc2_1$, Z = 8. The structure has been solved by direct methods using 1002 independent observed diffractometer measured intensities, [$|Fo| > 3\sigma(|Fo|)$, $2\theta < 116^\circ$, Cu-$K\alpha$ radiation]. There are two crystallographically independent molecules in the crystal each with slightly differing conformations. The maximum torsional difference between the two molecules is $\sim 20^\circ$. Skeletal and space-filling representations of the molecules are used to illustrate the spatial relationships of the reactive sites. The crystal packing and intermolecular hydrogen bonding interactions have been investigated.

(1) Burzynski, S.R. and Hai, T.T. (1985). Drugs of the Future, *10*, 103-105.

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STEREOCHEMICAL MODELING STUDIES OF DNA AND 3-N-PHENYLACETYLAMINO-2,6-PIPERIDINEDIONE

L.B.Hendry, T.G.Muldoon, Stereochemical Genetics, Inc. & Medical College of Georgia, Augusta, Georgia 30901 USA

Modeling studies in our laboratories have revealed that a variety of natural products exhibit stereochemical complementarity to DNA. The type and degree of complementarity has been used to predict biological activity (U.S. Patent 4,461,619). For example, the novel urinary dipeptide analog, 3-N-phenylacetylamino-2,6-piperidinedione (PAPD), can be inserted into DNA and forms a stereospecific hydrogen bond to a phosphate oxygen on the sugar-phosphate backbone. PAPD can be inserted between base pairs in several sequences; the order of preference is 5'-dTdA-3'·5'-dTdA-3'> 5'-dTdC-3'·5'-dGdA-3', 5'-dCdT-3'·5'-dAdG-3'> 5'-dTdG-3'·5'-dCdA-3'>> remaining sequences. These findings led us to predict that PAPD (which possesses no demonstrable toxicity) could interact reversibly with DNA and may compete with certain carcinogens for binding to DNA. If this scenario is correct, PAPD should exhibit antitumorigenic activity. Experimental studies reported here confirm our predictions; further development of this novel agent appears warranted.

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ANTINEOPLASTON A10 ACTIVITY IN RODENT MAMMARY TUMORS

T.G. Muldoon, J.A. Copland, L.B. Hendry, Stereochemical Genetics, Inc. and Medical College of Georgia, Augusta, Georgia 30912, USA.

Antineoplaston A10 is a potent antitumor agent produced in humans and therefore virtually non-toxic. In mice, this agent inhibits remarkably the rate of formation of spontaneous virus-induced mammary tumors. In rats, its effectiveness as a dietary supplement on occurrence of carcinogen-induced mammary tumors was examined. Using a single gastric intubation regimen of dimethylbenz(a)anthracene treatment to produce mammary tumors, we found that A10 blocked tumor formation for prolonged intervals, whether started 10 days prior to the DMBA or 70 days after DMBA (when tumors were appearing at a maximal rate in response to the carcinogen). This activity was dose-dependent on the dietary content of A10, 1% being optimal. In all cases, A10 inhibited appearance of new tumors, but did not cause regression of existent ones, thus having antitumorigenic, but not anticancer, activity. Only the estrogen-dependent fraction of the total mammary tumors present was sensitive to A10 inhibition, assessed by tamoxifen resistance and ovariectomy-induced patterns of regression. Surprisingly, this action appears to be independent of a mechanism involving estrogen receptor binding, since A10 has no measurable affinity for the rat uterine estrogen receptor. We are investigating the possibilities that A10 attenuates estrogen receptor activity indirectly at the nuclear functional acceptor level, or that this agent works through specific receptors of its own.

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SELECTIVE MONOAMINE OXIDASE TYPE B INHIBITION BY A NOVEL DIPEPTIDE ANALOG, PHENACYPERIDONE

B.I. Diamond*+, A. Hitri*+, D. Ewing*, L. Hendry*+, Department of Psychiatry and Medicine, Medical College of Georgia+ and Stereochemical Genetics, Inc.* Augusta, Georgia 30901 USA

Stereochemical modeling studies (U.S. PATENT 4,461,-619) predicted that the novel antitumorigenic dipeptide analog, 3-phenylacetyl-amino-2,6-piperidinedione (phenacyperidone, PAPD), would inhibit type B monamine oxidase (MAO) activity. Effects of PAPD on MAO type A and B were studied in vitro in human platelets as well as in rat and human brain tissue. Behavioral studies in vivo in male Sprague Dawley (200 g) were also conducted. Using C14 phenylethylamine (PEA) and C14 5-hydroxytryptamine (5HT) as substrates for MAO B and A respectively, PAPD preferentially inhibited type B MAO in both rat and human brain. Inhibition curves yield an IC50 in rat brain for type A activity of 93.3± 6x10-6M and B activity of 8±2.1x10-6M. Human Brain IC50 values were 138.6±15.1x10-6M for type A and 19.9 ±3.7x10-6M for type B. Moreover, type B MAO activity in platelets from normal volunteers was inhibited by PAPD with an IC50 value of 63.8x10-6M. PAPD in doses greater than 200 mg/kg potentiated PEA stereotype, the reversal of reserpine symptoms by PEA, and PEA turning in unilateral nigra lesioned rats. These effects were similar to deprenyl but not clorgyline administration to animals. These results demonstrate the preferential action of PAPD on MAO B activity. Since PAPD is safe in animals and man its use in CNS disorders may be fruitful.

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ACTIVE ANTICANCER COMPONENTS OF ANTINEOPLASTON FORMULATIONS.

M. C. Liau*, A. Ashraf*, S. R. Burzynski** - *Department of Biochemistry, **Department of Medicine - Burzynski Research Institute, Inc. - Stafford, Texas 77477, U.S.A.

Antineoplastons in urine are retained by C18 column at pH 2.5 (1). The urinary components retained by C18 can be eluted in succession with 40% methanol and 80% methanol. Both fractions possess good antitumor activity in the tissue cultures of human cancers. Active components present in 40% methanol eluant are weakly acidic peptides which are not reatined by DEAE-Sepharose column. Upon chromatography on polyacrylamide P2 column, two such components with K_{av} of 0.89 and 1.27 show good anticancer activity. A third component obtained by same procedures with K_{av} of 2.66 has been identified as riboflavin, which also shows anticancer activity. Active components present in 80% methanol eluant are strongly acidic peptides which are retained by DEAE-Sepharose eluted with 0.33M NaCl, dark pigments and organic acids. By adjustment of pH to 1.5, the dark pigments and organic acids become oily precipitates, whereas strongly acidic peptides remain in the supernatant. On polyacrylamide P2 column, these peptides are eluted in a fraction with K_{av} of 0.09. Organic acids in the precipitates can be separated from dark pigments by extraction with ethylacetate. Dark pigments have the highest specific activity to inhibit cancer growth.

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PHASE I CLINICAL STUDIES OF ORAL FORMULATION OF ANTINEOPLASTON A3.

S. R. Burzynski*, E. Kubove*, B. Burzynski+ - *Department of Medicine, +Department of Pharmacy - Burzynski Research Institute, Inc. - Stafford, Texas 77477, U.S.A.

Antineoplaston A3 (A3) underwent extensive human toxicology studies in the form of intravenous injections (1). Since A3 can be administered orally, it was very important to have a short additional Phase I study with A3 capsules which is described in this presentation. Clinical trials involved 11 patients diagnosed with: cancer of the prostate (7 cases), cancer of the ovary, kidneys, cervix and oligodendroglioma. Only patients with six weeks survival and who continued the treatment for at least six weeks, were eligible. A3 was administered orally daily in divided doses from 60 to 177 days, and the highest dosage was 122 mg/kg/24 hours. There were only 3 incidences of mild side effects observed including nausea and vomiting and flatulence. Desirable side effects included increase of red and white blood cells and platelet counts. 64% of patients had objective response to the treatment including cases of adenocarcinoma of the prostate and kidney. 27% of patients were classified as stable disease without objective improvement and 9% of patients had increasing disease. The oral administration of A3 is associated with minimal side effects, and is responsible for objective response in most of the patients included in the Phase I studies.

References

(1) Burzynski, S. R., Australian Patent No. 551109.