

## STEREOCHEMICAL MODELLING STUDIES OF THE INTERACTION OF ANTINEOPLASTON A10 WITH DNA

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**Summary:** Antineoplaston A10 (3-phenylacetyl-amino-2,6-piperidinedione), a peptide analogue originally isolated from human urine, has been demonstrated to fit between base pairs in DNA. Examination of the fit of A10 into the 10 possible sites in unwound DNA using published criteria revealed a preference, but not absolute specificity, for the sequence 5'-dTdT-3'·5'-dAdA-3'. Good fits were also observed for the sequences 5'-dTdC-3'·5'-dGdA-3' and 5'-dCdT-3'·5'-dAdG-3'. In each case at least one stereospecific hydrogen bond was possible between the imino proton of the piperidinedione ring stacked between the two pyrimidines and a neighbouring phosphate oxygen of the DNA backbone. These findings support the prediction that A10 may interact reversibly with DNA and thereby compete with carcinogens that form covalent linkages with DNA (e.g., arene oxides) (1). It follows that such interactions should prevent the growth of tumours induced by various carcinogens.

### Introduction

Antineoplaston A10, 3-phenylacetyl-amino-2,6-piperidinedione, is a modified dipeptide analogue originally isolated from extracts of human urine (1). A10 is a simple dehydration product of the known natural product phenylacetylglutamine which is formed *in vivo* by conjugation of phenylacetic acid and L-glutamine (2). This molecule has been reported to be one of several urinary components

that can inhibit the growth of certain cancer cells in culture (1).

In the original report of the isolation and identification of A10 (1), the authors speculated that the mode of action of this molecule might be different from that of classical antineoplastic drugs. The rationale for this was based upon the observation that A10 was structurally dissimilar to known chemotherapeutic agents such as actinomycin D, amsacrine or mitoxantrone. Moreover, unlike many chemotherapeutic agents, A10 and/or one of its hydrolysis products, phenylacetylglutamine, were natural products endogenous to humans. Studies in the authors' laboratories had demonstrated that A10 was capable of inserting between DNA base pairs in a stereochemically complementary fashion

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