

## Glossary of symbols

AFB	Aflatoxin B <sub>1</sub>
AP6	Cellular binding protein E6
AS2-1, AS5, AS2-5, A10, A10-1, A2, A3, A5	Antineoplastons AS2-1, AS5, AS2-5, A10, 'A10 Injections', A2, A3, and A5
BCR	Breakpoint cluster region
BCR-ABL	p210 BCR-ABL fusion protein
BP	Benzo[a]pyrene
CDK	Cyclin-dependent kinase
CMV	Cytomegalovirus
E6	Protein produced by HPV
EGF	Epidermal growth factor
Elk-1, Myc, Jun	Transcription factors
Erk-1, Erk-2	MAP kinases
GDP	Guanosine diphosphate
GNRF	Guanine nucleotide release factor
GRB2	Growth factor receptor-bound protein
GST	Glutathione S-transferase
GSTM1	GST- $\mu$ class gene
GSTP1	GST- $\pi$ class gene
GTP	Guanosine triphosphate
HPV	Human papilloma virus
IE84	CMV protein
IPP	Isopentenylpyrophosphate
MAPK	MAP kinase
MAPKK	MAP kinase kinase
NF-1	Neurofibromatosis type I tumor suppressor gene
PDGF	Platelet derived growth factor
PPM	5-pyrophosphomevalonate
PTK	Protein tyrosine kinase
p21	p21 <sup>ras</sup> protein
p53	p53 gene
Raf	Raf serine threonine kinase
Rb	Retinoblastoma gene protein

## 1.2 Classification of Antineoplastons and Mechanisms of Action

Antineoplastons are divided into 2 groups. One group has a broad spectrum of activity and consists of A1, A2, A3, A4, A5, A10, A10-1, AS2-1, AS2-5, and AS5. The second group consists of antineoplastons H, L, O, F, Ch and K, each of which show selective activity against just one type of neoplasm.<sup>[2,10]</sup> Synthetic A10, A10-1, AS2-1, and AS2-5 are derivatives of glutamine, isoglutamine, and

phenylacetate, and AS5 is phenylacetate.<sup>[13-15]</sup> Antineoplastons are multifunctional agents with a number of different mechanisms of activity.

AS2-1, AS2-5, AS5, and A10-1 inhibit incorporation of glutamine into the proteins of neoplastic cells, which may cause G<sub>1</sub> phase arrest of abnormal cells.<sup>[12,16-19]</sup>

The mechanism of activity of A10 involves intercalation with DNA. Favoured sequences of DNA are those which interact with known carcinogens, such as benzo[a]pyrene and aflatoxin B<sub>1</sub>.<sup>[13,20-25]</sup>

A2, A3, A5, AS5, and AS2-1 inhibit methylation of nucleic acids in abnormal cells.<sup>[26-28]</sup> During human life, certain genes are activated and others deactivated by methylation of DNA.<sup>[29]</sup> Hypermethylated genes, such as the gene for haemoglobin F in adults, are not active.<sup>[30]</sup> Genomic imprinting, which relies on methylation of the gene, can cause the same genetic disorder as mutation.<sup>[31,32]</sup> Hypomethylation of the genes offers a great promise in inhibition of cancer growth and in control of genetic disorders.<sup>[30,33-38]</sup> Unblocking of NF-1 and NF-2 is indicated by positive response in the treatment of neurofibromatosis.<sup>[39]</sup> The tumour suppressor genes, NF-1, p53 and Rb, could be blocked because of hypermethylation and activated again by antineoplastons.

Abnormal expression or mutation of *ras* family oncogenes plays a crucial role in pathogenesis of most important cancers. The product of *ras* oncogene p21 is a 'master switch' that decides if the cell will differentiate and die or multiply and produce cancer. The crucial reaction in the process of isoprenylation, similar to cholesterol biosynthesis, is blocked by AS5 and AS2-1 thus deactivating p21 (fig. 1).

p53, NF-1, and Rb genes are found to have deficient function in most cancers.<sup>[55]</sup> In addition to mutation, the expression of the genes can be blocked through hypermethylation.<sup>[31,32,56]</sup>

Hypomethylation by A2, A3, A5, AS2-1, and AS5 may activate tumour suppressor genes, while A10 protects against the action of carcinogens (fig. 2).

GSTs conjugate carcinogens to glutathione. Patients with cancer of the prostate, lung, bladder,