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# NOVEL SELECTIVE NONTOXIC ANTICANCER AND ANTIVIRAL AGENTS

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Selective targeting to diseased cells, ensuring nontoxicity for normal cells, are the master words for anticancer and antiviral therapies. Yet little progress has been made on these lines and adverse side effects are still the rule.

After having designed a rapid and simple in vitro screening test (Oncotest), we were able to find a number of plant derived, chemically well defined substances which selectively inhibit cancer cell multiplication without affecting normal cells. Activity of these agents is based on the fact that, as we discovered after extensive comparison of DNAs from cancer cells and their normal counterparts, cancer DNA is characterized by its highly relaxed, destabilized secondary structure, within which H-bond breakage is evidenced by 260 nm UV absorption, always distinctly higher than that of normal DNA. Our anticancer agents easily bind to the "open" cancer DNA chains; in contrast, they do not bind to normal DNA chains, which are "closed" most of the time.

In mice bearing Ehrlich ascitis or YC8 lymphoma, our anticancer agent BG-8 (alstonine), by the interaperitoneal route, ensured a 50-60% three month survival. If BG-8 was used together with radiotherapy or chemotherapy (which, as we showed, enhances binding of the anticancer agent by further opening cancer DNA chains), three months survival reached 100%. Monotherapy with another of our anticancer agents, PB-100 (flavopereirine), induced a 75-90% survival.

In humans, BG-8 was then applied by a number of physicians to various malignancies, such as breast cancer and advanced prostatic carcinoma, with good results and no adverse side effects. PB-100, which crosses the blood-brain barrier, has moreover been applied to brain tumors, together with radiotherapy, inducing total or partial regression or enclosure of the malignancy within a well defined boundary.

Lately, our in vitro studies using PB-100 confirmed its possibilities regarding brain tumors. At  $\mu\text{g/ml}$  concentrations, PB-100 can kill over 98% of BCNU-resistant human glioblastoma cells (U 251), whilst not affecting normal control cells (CRL 1656 astrocytes). PB-100 checks excessive mitogenic effects of physiological molecules such as interleukins (particularly IL-6), catecholamines, steroid hormones, ferritin. It concentrates in the nucleus, and especially the nucleoli, of glioblastoma cells but does not enter normal astrocytes.

In nucleic acids, PB-100 binds to G and A rich clusters, which are common, for instance, near DNA initiation sites or in important RNA loop sequences. This explains how PB-100 also comes to have extensive antiviral properties. By binding to viral DNA or RNA G and A rich clusters, it stands in the way of viral replicating enzymes, including retrovirus reverse transcriptase. PB-100 antiretroviral activity and lack of toxicity for non-infected cells was demonstrated in vitro and in humans, notably by a clinical trial on HIV-infected patients.