Introduction and Overview

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Camptothecin made its beginnings as an anticancer drug over thirty years ago. Unfortunately, it started on the wrong leg because, as we now know, the sodium salt used then for patient administration is inactive as far as anticancer activity is concerned, and highly toxic for the patient because of the opening of the lactone ring, necessary for its pharmacological action.

Camptothecin then went into eclipse for over twenty years, until the late eighties when interest in it was revived by the finding that some of its derivatives were highly active against murine tumors and xenografts of human tumors in nude mice. Two main classes of camptothecin derivatives have been developed: water-soluble compounds administered intravenously and water-insoluble compounds mostly given orally. Representatives of both classes have been brought to clinical trials and are being tested into a rapidly increasing number of patients now. Antitumor effectiveness has been found against numerous tumor types and the list is increasing in length everyday. Toxicities, which vary from compound to compound, appear to be manageable. Scheduling in every case is of crucial importance. It appears that camptothecins have to be administered continuously for prolonged periods of time in order to be effective. From experimental studies *in vitro* and *in vivo*, it is quite evident that these compounds are cytostatic for prolonged periods of time before becoming cytotoxic. Any interruption of treatment before this stage is reached is likely to compromise the final outcome of treatment, allowing the tumor to make good its losses.

We are still far from having reached optimization of treatment of camptothecins as single drugs and much farther away from the optimization of combination treatment which is now in its infancy with these drugs. Camptothecins are just beginning to be combined with chemotherapeutic agents or other therapeutic modalities. It should be noted, however, that experimental results indicate the possibility of synergism between camptothecins and radiotherapy. This is particularly interesting in view of the fact that camptothecins are, in animal models, very active against cerebral tumors. The possibility exists of using the association of camptothecin treatments with head irradiation for primary and metastatic brain tumors.

Interest in these compounds is growing exponentially as indicated by the number of publications on the subject.

The main difficulty confronting us now goes back to the beginning of camptothecin; then it was man-made, now its nature's product. Camptothecin failed at the beginning because it was transformed into the inert sodium salt for solubilization purposes. Now we introduce camptothecin and its derivatives into the body as closed lactone ring, gaining some effectiveness over the salt. Unfortunately, it has been shown that at physiological pH, the ring opens and such an opening is catalyzed by serum albumin. It appears also that human serum albumin is much more effective in opening the ring than mouse albumin. The consequence is that

the anticancer results obtained in mice against human tumors are superior to what is obtained in clinical trials treating human tumors in the human body. We must try to overcome this shortcoming, either by chemical modification of the molecules involved, by complexing them with protective chemicals, or by manipulating their delivery. Every effort has to be made to keep the lactone ring closed in order to transform these compounds from effective anticancer agents into the extraordinarily effective agents that they are already in the mouse. It has to be remembered that these compounds in nude mice are curative for all the human tumors tested, 36/36, which cover the majority of human neoplasms. However, in mice, 55% of the drug present in the blood during its biological life is in the close lactone ring form. These same compounds in man are active but not as spectacularly as in mice. This is not surprising when we consider that under the same conditions of administration, the percentage of the drug present in human blood during its biological life is 3%, as repeatedly measured in several patients. Indeed, it is proof of the extraordinary potential anticancer activity of this class of drugs that we can detect any cancer inhibition in humans. This has been observed however, and camptothecins, as they are, already can be considered very effective antitumor agents. Let us hope that we can rapidly make them even more effective. This meeting should contribute much to this goal.

During the next three days, you will hear important contributions to the chemistry, biology, pharmacology and clinical investigations of camptothecins by the best scientists and clinicians specializing in this field. To all of you go my best wishes for a very productive and successful meeting.