CYTOTOXIC ANTICANCER DRUGS: MODELS AND CONCEPTS FOR DRUG DISCOVERY AND DEVELOPMENT

edited by
Frederick A. Valeriote
Thomas H. Corbett
Laurence H. Baker

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DRUG DISCOVERY - 1990

Frederick Valeriote, Thomas Corbett and Laurence Baker

This is the first of what we hope will become a regular meeting held on the alternate years of the EORTC-NCI joint European (Amsterdam) meeting. Our focus is on the presentation and discussion of cytotoxic agents, with a significant portion of the Symposium to include the exciting frontiers of drug discovery being explored by the National Cooperative Drug Discovery Groups (NCDDG) Program. Like most areas of cancer research, cytotoxic research has gone through its ups and downs. A few years ago, with the lack of active agents coming through the pipeline, together with the excitement concerning new modalities and new approaches such as biological response modifiers, immuno-conjugates, hyperthermia, radiation sensitizers, biochemical modulation and antisense therapy, both expectation about finding new cytotoxics, and subsequently funding, waned and the number of new cytotoxics declined significantly. We are now observing a redressing of this problem and a more balanced national approach. Of significance this year has been the initiation of renewed efforts in the area of natural product drug discovery. While the entire field of Developmental Therapeutics (including both Experimental and Clinical Therapeutics) has many potentials for discovery of curative therapy, the area of discovery of new cytotoxics is particularly promising at present.

There have been a number of major changes during the past decade in research on drug discovery of cytotoxic agents. For over 30 years, from the inception of an organized drug discovery program, murine leukemia cells (specifically P388 and L1210

lymphocytic leukemias) *in vivo* or KB cells *in vitro* were the foci and funnel of cytotoxic research programs which not only discovered new active agents but also defined the direction of analog synthesis. Increased therapeutic efficacy was defined in terms of greater increase in lifespan of the leukemia-bearing mice at the drug's maximal tolerated dosage. The success of this program can be assessed by the discovery of a host of agents active against lymphocytic leukemia and lymphoma. By the standard of the murine leukemia models finding drugs effective against the human tumor counterparts, the program was successful. The frustration and subsequent decline in funding of the program resulted not from having cured human leukemias but from its inability to discover major leads against human solid tumors. Cure rates for cancers of the lung, breast, colon and pancreas did not seem to budge following treatment with the alphabet soup of drugs which became available from this leukemia-based drug discovery program.

The poor record of discovery of new structural leads during the 1970's, and especially the dearth of agents active against solid tumors, led to a re-thinking of the underlying screen. As evidenced by the first two presentations in this Symposium, a radical break with the past occurred in the early 1980's and emphasizes the present screening philosophy: "You get what you fish for!" As shown in Figure 1A, if you use leukemia cells as your screening "bait", you will pull out antileukemic agents. Figure 1B, by analogy indicates that if you use solid tumors you will find agents active against solid tumors. Further, and most important, it seems that there may be little overlap between the specific compounds most effective against either tumor type.

Some investigators believed that since we are searching for agents active against human solid tumors, then the human tumors must be the bait on the hook. Use of human tumors directly from the patient has been attempted but is technically difficult and expensive for a primary screen. Also, there is a problem of reproducibility since each specimen is consumed quickly so that there is no "standard" from one run to the next. As discussed in this Symposium, their use in a Phase 2 setting is profitable. A

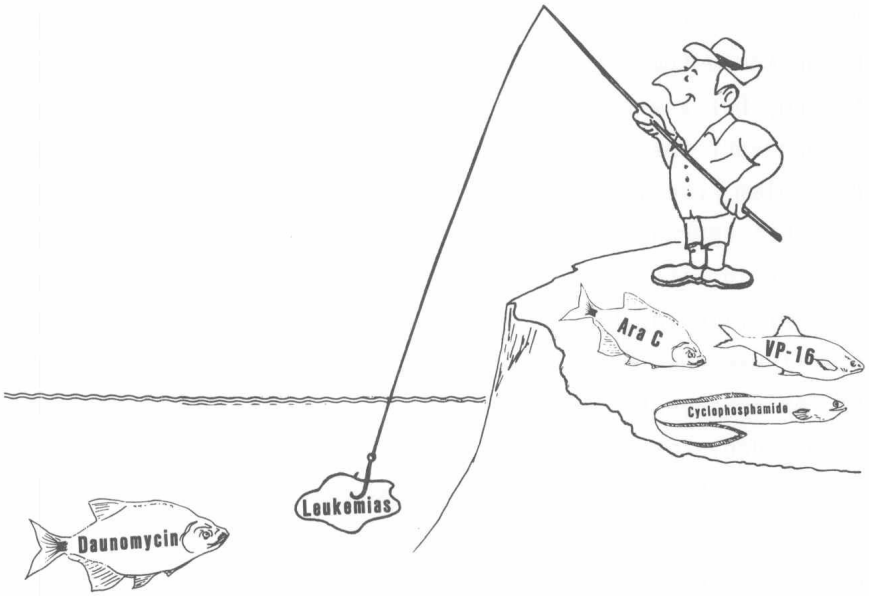

Figure 1A. Cartoon of present anticancer screening philosophy for antileukemic agents.

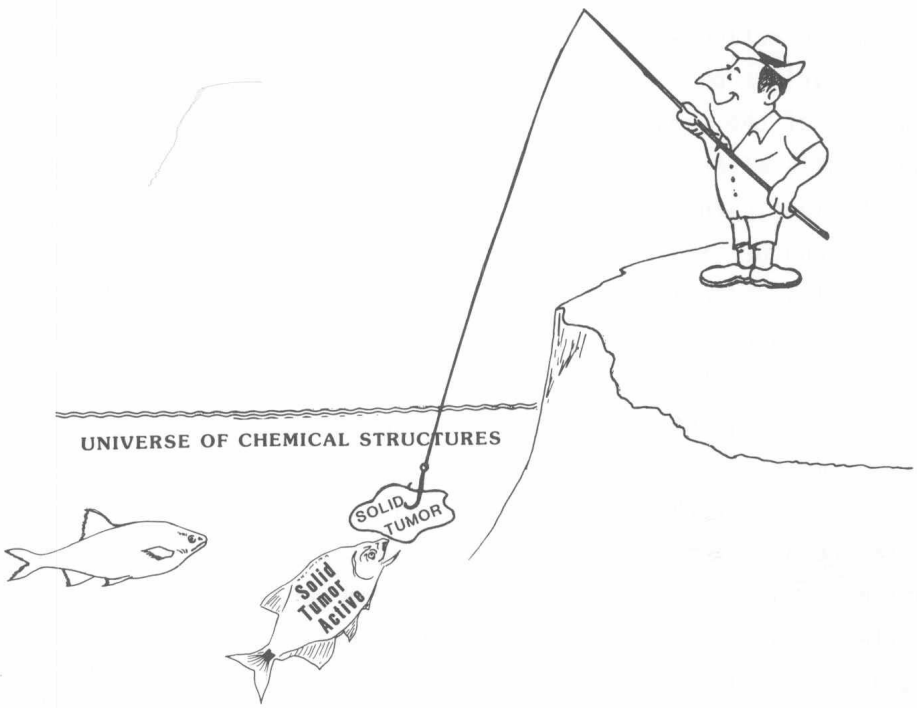

Figure 1B. Cartoon of present anticancer screening philosophy for solid tumor selective agents.