1. INTRODUCTION

L1210 and P388 leukemias were developed in 1948 (1) and 1955 (2), respectively. Each leukemia played an important role in both screening and detailed evaluations of candidate anticancer agents. Fifty years later, these in vivo models are still used to evaluate anticancer activity, although at a greatly reduced level. This chapter reviews their past and present role in the evaluation of anticancer drugs. Data on the sensitivity to clinically useful drugs of these two leukemias and the drug-resistant P388 sublines are reported.

2. ROLE IN DRUG SCREENING

The use of murine leukemias in drug screening had its beginning in the 19th century (3). It was at this time that studies of rodent tumors were being conducted that would pave the way for large-scale drug screening programs. Although spontaneous tumors in animals were used as models, it was the ability to transplant tumors that made possible the development of tumor systems that could be used both for large-scale screening and detailed evaluations of candidate anticancer agents. Furthermore, the development in the 1920s of inbred strains of mice allowed the successful transplantation of numerous tumor systems (4).

By the 1940s, it was recognized that systemic cancer would respond to drug treatment. As a result, drug discovery programs were begun at several institutions in the United States and abroad. Soon anticancer drug screening programs were initiated, one of which
was the Memorial Sloan-Kettering program that used the mouse sarcoma 180 (SA-180) as its screening model. Since additional drugs exhibited some anticancer activity and the supply of new candidate agents exceeded the screening capacity, the need for a national drug development program became apparent. In 1954, Congress directed the National Cancer Institute (NCI) to start such a program, and in 1955, the Cancer Chemotherapy National Service Center (CCNSC) was created.

The initial CCNSC screen consisted of three mouse tumors: L1210 leukemia, SA-180, and mammary adenocarcinoma 755 (5). Over the years, the primary screen changed from the original three tumors to L1210 plus two arbitrarily selected tumors to L1210 plus Walker 256 carcinosarcoma to L1210 plus the P388 leukemia to L1210 plus P388 plus B16 melanoma or Lewis lung tumor (6). Secondary evaluations of the most promising agents were conducted in a variety of other tumor models.

In 1976, a major change occurred in the NCI primary screen. The new screen consisted of a panel of colon, breast, and lung tumor models (murine and human); however, drugs were initially screened in P388 leukemia (7).

The low number of drugs with marked activity against human solid tumors led to a radical change in the screening program that had used murine leukemia models. In the mid-1980s, the NCI developed a new screen based on the use of established human tumor cell lines in vitro (8). The two screening systems were to be conducted in parallel so as to permit a comparison; however, in early 1987, budget cuts forced an end to large-scale P388 screening (9).

3. CHARACTERISTICS

L1210 and P388 leukemias were both chemically induced in a DBA/2 mouse by painting the skin with methylcholanthrene (1,2). The leukemias are propagated in DBA/2 mice by implanting ip 0.1 mL of a diluted ascitic fluid containing either 10^5 (L1210) or 10^6 (P388) cells. Testing is conducted in a hybrid of DBA/2 (e.g., CD2F1 or B6D2F1). Implant sites that are frequently used are ip, iv, or ic. For L1210 leukemia (10^5 cells), the median days of death and the tumor doubling times for these implant sites are 8.8, 9.9, 6.4, and 7.0 and 0.34, 0.46, 0.45, and 0.37 d, respectively. For P388 leukemia (10^6 cells), the median days of death and the tumor doubling times for these implant sites are 10.3, 13.0, 8.0, and 8.0 and 0.44, 0.52, 0.68, and 0.63 d, respectively.

Studies on the rate of distribution and proliferation of L1210 leukemia cells were conducted at Southern Research by Skipper and coworkers (10) using bioassays of untreated mice after ip, iv, and ic inoculation. After ip inoculation, most of the L1210 cells were found in the ascites fluid of the peritoneal cavity. On the median day of death from the leukemia, the most infiltrated tissues were the bone marrow, liver, and spleen. After iv inoculation, most of the L1210 cells were filtered out in the bone marrow. On the median day of death from the leukemia, the most infiltrated tissues were also the bone marrow, liver, and spleen. After ic inoculation, most of the L1210 cells remained in the brain (for 3–5 d). On the median day of death from the leukemia, the spleen was heavily infiltrated. (The extent of the leukemia in other tissues was not reported.)

At Southern Research, antitumor activity is assessed on the basis of percent median increase in life span (% ILS), net log_{10} cell kill, and long-term survivors. Calculations of net log_{10} cell kill are made from the tumor doubling time, which is determined from an