Human Tumor Xenograft Models in NCI Drug Development

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SUMMARY

1. INTRODUCTION

The preclinical discovery and development of anticancer drugs by the NCI consist of a series of test procedures, data review, and decision steps that have been summarized recently (1). Test procedures are designed to provide comparative quantitative data, which in turn, permit selection of the best candidate agents from a given chemical or biological class. Periodic, comprehensive reviews by various NCI committees serve not only to identify and expedite the development of active lead compounds that may provide more efficacious treatments for human malignancy, but also to eliminate agents that are inactive and/or highly toxic from further consideration.

Various components in NCI's drug discovery and development process have evolved in response to a combination of factors—scientific, clinical, technological, and fiscal. A series of review articles have charted the evolution of the drug screening program and have described specific elements of the process, e.g., acquisition, screening, analog development and testing, pharmacology, and toxicology (2–12). The present chapter provides: a brief history of the in vivo screens used by NCI; a description of the human tumor xenograft systems, which are currently employed in preclinical drug development; a discussion of how these xenograft models are employed for both initial efficacy testing as well as detailed drug evaluations; and a description of a new model that may facilitate preclinical drug development.
2. HISTORICAL DEVELOPMENT OF NCI SCREENS

Analyses of various screening methods available prior to 1955 indicated that (1) nontumor systems were incapable of replacing tumor systems as screens, and (2) no single tumor system was capable of detecting all active antitumor compounds (13). Since that time, the preclinical discovery and development of potentially useful anticancer agents by the NCI have utilized a variety of animal and human tumor models not only for initial screening, but also for subsequent studies designed to optimize antitumor activity of a lead compound or class of compounds. Although the various preclinical data review steps and criteria have remained essentially the same throughout the years, the modes and rationale of in vivo testing employed by NCI have evolved significantly.

2.1. Murine Tumor Screens, 1955–1975

In 1955, NCI initiated a large-scale in vivo anticancer drug screening program utilizing three murine tumor models: sarcoma 180, L1210 leukemia, and carcinoma 755. By 1960, in vivo drug screening was performed in L1210 and in two additional rodent models selected from a battery of 21 possible models. In 1965, screening was limited to the use of two rodent systems, L1210 and Walker 256 carcinosarcoma. In 1968, synthetic agents were screened in L1210 alone, whereas natural product testing was conducted in both L1210 and P388 leukemias. A special testing step was added to the screen in 1972 to evaluate active compounds against B16 melanoma and Lewis lung carcinoma. It is noteworthy that this first 20 years of in vivo screening relied heavily on testing conducted in the L1210 model.

2.2. Prescreen and Tumor Panel, 1976–1986

In late 1975, NCI initiated a new approach to drug discovery that involved prescreening of compounds in the ip-implanted murine P388 leukemia model, followed by evaluation of selected compounds in a panel of transplantable tumors (14). The tumors in the panel were chosen as representative of the major histologic types of cancer in the US and, for the first time in NCI history, included human solid tumors. The latter was made possible through the development of immunodeficient athymic (nu/nu) mice and transplantable human tumor xenografts in the early 1970s (15,16). Beginning in 1976, the tumor panel consisted of paired murine and human tumors of breast (CD8F, and MX-1), colon (colon 38 and CX-1 [the same as HT29]) and lung (Lewis and LX-1), together with the B16 melanoma and L1210 leukemia used in previous screens.

The majority of the early NCI testing conducted with the human tumors used small fragments growing under the renal capsule of athymic mice. The subrenal capsule (src) technique and assay were developed by Bogden and associates (17). Although labor-intensive, the src assay provided a rapid means of evaluating new agents against human tumor xenografts at a time when the testing of large numbers of compounds against sc xenografts seemed untenable. As experience was gained with the husbandry of athymic mice, longer-duration sc assays became manageable.

A detailed evaluation of the sensitivities of individual tumor systems employed from 1976–1982 revealed a wide range in sensitivity profiles as well as “yield” of active compounds (14). The data clearly indicated that rodent models may not be capable of detecting all compounds with potential activity against human malignan-