Human Tumor Xenografts and Explants

Heinz-Herbert Fiebig, MD, PhD, and Angelika M. Burger, PhD

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1. INTRODUCTION

1.1. Historical Perspective

Since the first report of the successful xenografting of a human tumor into nude mice in 1969, there have been numerous studies conducted throughout the world using the nude mouse as a tool to answer a variety of questions regarding the cause, prevention, and therapy of cancer. Thus, the role of immunodeficient animals in oncology has continuously increased, and the athymic nude mouse has proven to be an outstanding host for many human solid-tumor xenografts (1,2). These mice are now extensively used in the development of potential anticancer drugs, new antineoplastic treatment modalities, and studies of tumor biology (3–7). Moreover, mice with severe combined immunodeficiency (SCID) have enlarged the spectrum of possible applications in cancer research and enabled engraftments of human tumors that were previously difficult to explant, such as those of the hematopoietic system (8).

Prior to the discovery of immunodeficient mice, syngeneic transplantable mouse tumor systems or autochthonous rat tumors were employed as the main—or the only—tools in the development of antitumor agents (5,7,9). Most of the chemotherapeutic agents currently used in the clinic have been developed in these rodent tumor models (reviewed in chapters 1–4). The most frequently used murine tumors were the leukemias L1210 and P388, the melanoma B16, and the Lewis Lung cancer (LLC) model. Yet the classes of agents found active in the mouse tumor models, however, were limited, and mainly comprise alkylating agents, and some other DNA interacting drugs (5,10,11).
Table 1

Human Tumor Xenograft Models Established in Freiburg (XFs)

- more than 1600 tumors of cancer patients have been sc-implanted into nude mice
- more than 300 human tumors of the following tumor types have been established:

<table>
<thead>
<tr>
<th>Tumor Type</th>
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<tbody>
<tr>
<td>bladder</td>
<td>breast</td>
<td>colon</td>
<td>cervix uteri</td>
</tr>
<tr>
<td>CNS</td>
<td>gall bladder</td>
<td>lung</td>
<td>head and neck</td>
</tr>
<tr>
<td>leukemias</td>
<td>liver</td>
<td>lymphoma</td>
<td></td>
</tr>
<tr>
<td>melanomas</td>
<td>pleura mesothelioma</td>
<td>ovarian</td>
<td></td>
</tr>
<tr>
<td>pancreas</td>
<td>prostate</td>
<td>renal</td>
<td>sarcoma</td>
</tr>
<tr>
<td>stomach</td>
<td>testicle</td>
<td>thymoma</td>
<td>uterus</td>
</tr>
</tbody>
</table>

60 models have been well characterized (see following tables)

Nevertheless, today transplantable syngeneic murine-tumor models remain particularly valuable for studying biological response modifiers or certain agents that need to be evaluated in a syngeneic environment, such as those targeting distant organ metastasis (9).

In the late 1980s and early 1990s, new drug development moved from applying general cytotoxic principles to molecular target-directed treatment strategies (12). Consequently, there was a need to identify tumor types/individual patient tumors that express the target and could benefit from more selective therapies in phase II/III clinical trials. Thus, the in vivo models used in preclinical development today are “disease-oriented” and target-characterized, and are either human-tumor explants/xenografts or specifically bred transgenic mice (13). However, because of their high running costs and limited availability, transgenic mice are not suitable for large-scale drug testings. Thus, xenografts/human explants have become the gold standard in cancer-drug development. Their use is highly recommended by regulatory agencies such as the EMEA (European Agency for the Evaluation of Medicinal Products) in the “note for guidance on the pre-clinical evaluation of anticancer medicinal products” (14).

1.2. The Strength of Human Xenografts Derived from Patient Explants

Whilst the spectrum of transplantable and autochthonous murine tumor models is confined to certain entities such as melanoma, colon, breast, bladder, or lung carcinomas, and genetically engineered mouse models cannot cover all human cancers, patient explants and stably growing xenografts derived thereof can be generated from the vast majority of malignancies. Table 1 shows the broad panel of human tumor types included in the Freiburg xenograft collection.

Moreover, the use of fresh surgical patient material or human-tumor engraftments growing subcutaneously in nude mice enable chemosensitivity screening procedures in vitro and in vivo, and thus can be used to predict clinical response (10,15-17). Human-tumor xenografts established in serial passage have demonstrated a particularly high correlation of drug response compared to that in the clinic (Table 2). If evaluated in the nude mouse in vivo the correct prediction for response (positive predictive value) was 90% (16,17). If tested in vitro using the clonogenic assay, the correct prediction was 60%. The prediction for resistance was 97% in vivo.