Synopsis of a Roundtable on Validating Novel Therapeutics for Multiple Myeloma

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Abstract

Purpose: With the identification of new molecular targets and pathways, many new therapeutic approaches are being identified for potential application in the treatment of multiple myeloma. New chemical compounds and biologics have been developed against molecular targets with substantial scientific evidence that these targets are involved in myeloma development, progression, or relapse. To safely and rapidly bring these advances to bear on the disease, new preclinical models in cells and animals need to be established, as well as prioritization and standardization in current preclinical and clinical validation. An experts’ roundtable was convened in November 2005 to discuss shortcomings in current preclinical models and discuss what models are needed to best validate therapeutics and combinations of therapies for multiple myeloma.

Conclusions: This exciting event brought together experts in compound validation, preclinical development, and experts in multiple myeloma from academic institutions and the pharmaceutical and biotechnology industries. The goals were to evaluate an algorithm for therapeutic validation and discuss in vitro modeling for target discovery, animal models for preclinical development, and models for testing drug combinations.

Multiple myeloma is a plasma cell malignancy that runs a progressive clinical course characterized by skeletal destruction, renal failure, infection, hypercalcemia, and anemia. Although new treatments have improved the outlook for patients with multiple myeloma, it remains an incurable disease with a median survival following conventional chemotherapy of ~4 years (1, 2). Multiple myeloma displays a low proliferation rate and often develops resistance to standard chemotherapeutic agents and radiation therapy (3). Resistance is primarily believed to be due to a block in drug-induced programmed cell death. Multiple myeloma cells avoid apoptosis by both intrinsic and extrinsic factors, such as through extracellular growth signals and the tumor microenvironment (4, 5).

Tumor progression in multiple myeloma is a multistep process involving changes in the microenvironment, including the induction of angiogenesis and the suppression of cell-mediated immunity, and multiple myeloma cells develop paracrine signaling loops involving cytokines and growth factors (6). Advances in our understanding of these changes have elucidated several targets against which dozens of new compounds and biologics are believed to be under development as possible therapies. In the myeloma microenvironment, including cell adhesion–mediated drug resistance (CAM-DR) models (7). An additional model termed extracellular matrix drug resistance (EM-DR) uses bone marrow stromal, cytokines, and extracellular matrix to recapitulate the multiple myeloma microenvironment (8). The third step is to test on primary patient specimens where possible. After in vitro testing has been conducted, novel therapeutics should be tested in multiple myeloma animal models. Potency should not be assessed in cell model systems but rather should be assessed in animal models and in patients. The strengths and weaknesses of current in vitro and in vivo multiple myeloma models were discussed at the roundtable and highlights were presented in this article.

In vitro Modeling for Target Discovery

Primary tumor samples are useful for examining characteristics of a patient’s own tumor; however, due to a limited supply, these samples are not sufficient for all of the molecular analyses and characterization needed for drug development. Cell lines derived from patient tumors that can be perpetuated in the laboratory provide a resource for drug development, albeit...
an imperfect replication of human multiple myeloma, an abundant supply of cells, the ability to share among multiple institutions, and with a diverse range of multiple myeloma characteristics represented. Weaknesses include that cell lines evolve over time and acquire mutations that are not present within a patient with multiple myeloma and that not all heterogeneity observed in patients has been established in cell culture models. Cell culture systems provide a beginning step for screening novel compounds for activity in multiple myeloma and should be followed with models in intact animals. 

Existing cell lines do not model the heterogeneity seen in multiple myeloma

When using multiple myeloma cell lines in testing new therapeutics, one must select a line that expresses the targets under study. Multiple myeloma is a heterogeneous disease and cell lines have been derived from many different patients representing many forms of the disease (Table 1). Table 1 provides a list of the most commonly used cell lines in multiple myeloma and some of their unique characteristics (5, 7, 9–11). Nearly half of multiple myeloma tumors are nonhyperdiploid and usually have one of five recurrent IgH translocations (12–14). Common partner chromosomes seen in multiple myeloma tumors are represented in the cell lines, including the 11q13 (CCN D1), which is seen in 16% of multiple myeloma tumors and is the most frequently detected known translocation. In addition, translocations seen in tumors and represented in cell lines involve the 4p16 (FGFR3 and MMSET), 16q23 (MAF), 6p21 (CCN D3), and 20q12 (MAFB), representing 15%, 5%, 3%, and 2% of tumors, respectively (15–18). It should be noted that there are virtually no multiple myeloma cell lines representing the hyperdiploid D1 group. The reasons no hyperdiploid multiple myeloma cell lines have been established are unclear, but it is
likely the early-stage tumors represented in this group are dependent on the bone marrow milieu and therefore a challenge to establish lines in culture. In contrast, the vast majority of existing multiple myeloma cell lines came from non–bone marrow origins, including pleural effusions and peripheral blood of patients with advanced stage disease, after tumor cells have spread outside the bone marrow microenvironment.

The diversity of currently available cell lines do capture the five common translocations and, additionally, have in some instances acquired their own additional abnormalities. For example, multiple myeloma cells in patients do not usually divide rapidly, but all the existing multiple myeloma cell lines do so. Therapeutics that target cell division and thus require rapid cell turn over may work well in the multiple myeloma cell culture model but not in patients. This is true for vincristine, which shows efficacy against nearly all multiple myeloma cell lines but has not worked well in multiple myeloma patients. Other shared characteristics include frequent RAS-activating mutations observed in multiple myeloma cell line and patients. Cell lines diverge from characteristics observed in multiple myeloma patients with the vast majority of cell lines carrying inactivating mutations in p53, rarely observed in patients. Another issue of concern is that many multiple myeloma lines publicly available are EBV positive and not representative of human multiple myeloma because few human multiple myeloma tumors express EBV.

The CAM-DR model shows that cell adhesion stimulates pathways mediating cytotoxic drug resistance in myeloma cells. Integrin-mediated fibronectin adhesion correlated with decreased response to the chemotherapeutic drug doxorubicin and a link between α4 integrin heterodimers and drug resistance was observed (7). The EM-DR model shows both cell-cell interactions between multiple myeloma cells and bone marrow stromal cells, as well as soluble factors produced by these interactions, play a role in drug resistance. The soluble factors in the EM-DR model were additive to the protective effects of direct cell-cell contact in myeloma cells, preventing drug-induced apoptosis (8). Although the mechanisms have not been entirely elucidated, the cell-adhesion model, as well as extracellular matrix, and soluble factors model provide important tools for assessing drug resistance.
In summary, although numerous cell lines and in vitro models exist for doing in vitro studies in multiple myeloma, several existing cell lines have acquired their own mutations that are not confirmed to exist in multiple myeloma patients or the cell lines are EBV positive. In addition, there is a shortage of cells derived from early-stage patients and a shortage of cell lines with known resistance to novel agents being used to treat multiple myeloma. New therapeutics should be tested against a panel of multiple myeloma cell lines encompassing the heterogeneity of the disease.

Standardization is needed for future development of in vitro models

For future drug development in vitro, it is recommended that laboratories establish standard assays of cell lines, such as HLA typing, EBV testing, PCR fingerprinting, and/or cytogenetic and karyogenetic measures to ensure that the lines retain their essential characteristics over time (19). In addition, assays using coculture with primary bone marrow stroma are encouraged. Coculture assays model the microenvironment and need to be refined and miniaturized for possible use in high-throughput screening (HTS) systems. Assessing the effect of novel therapeutics in cell lines and cocultures should be done in a context of agents with a known effect, and using cell lines with known resistance, and in the CAM-DR/EM-DR-resistant model systems (7, 8, 20). This could include routine testing with dexamethasone, doxorubicin, mitoxantrone, vincristine, or 5-fluorouracil. The next stages after in vitro assays should include (a) testing novel therapeutics in myeloma line models and (b) possibly using patients as models of their own disease.

Animal Models for Therapeutic Validation in Multiple Myeloma

Preclinical animal models for myeloma include (a) models of mouse myeloma and (b) xenograft models of human myeloma into mice (21–25). As shown in Table 2, murine models include the spontaneous 5T2MM and 5T33MM, which are transplantable mouse myeloma cells that can transfer disease in syngeneic hosts, and a newer mouse myeloma model with ABL-MYC retroviral induction in BCL-x(L) transgenic mice, leading to plasma cell tumors (26). The xenograft models shown in Table 2 include a variety of severe combined immunodeficient (SCID)-Hu, nonobese diabetic (NOD)/SCID, and SCID-Rab models (24, 25, 27). Each of these model systems has strengths and weaknesses, including differences in immunocompetency, disease onset, duration and tumor burden, and varying similarities to human multiple myeloma.

Models of mouse myeloma

The spontaneous 5TMM includes a series of mice derived from the original aged C57BL/KaLwRij strain that spontaneously developed myeloma, and the lines are maintained by in vivo transfer to young syngeneic mice (26, 28). The 5T2MM and 5T33MM are the best characterized and have been reported to have clinical characteristics similar to human disease, including localization of multiple myeloma cells to the bone marrow, measurable M-protein in serum, induction of osteolytic bone disease, and increased angiogenesis in the marrow (see Table 3). Both are useful models for testing therapeutic agents and allow for testing therapeutics that affect multiple myeloma cell homing, before disease onset or after the onset of overt disease (see Fig. 2). Therapeutic compounds or biologics can be tested at different time points in the disease model. For instance, as shown in Fig. 2, therapeutics can be delivered simultaneously at the time of transfer of multiple myeloma cells or delivery can be delayed until overt disease is established. Alternatively, the models allow for continuous treatment with therapeutics or testing of preventive agents before onset of overt disease.

Zoledronic acid treatment, beginning at the time of detectable paraprotein, prevents the development of osteolytic bone lesions, inhibits tumor growth, and increases survival in 5T2MM mice (29). Similarly, the cyclophilin picropodophyllin inhibitor of the insulin-like growth factor-I (R) tyrosine kinase inhibits insulin-like growth factor-I-stimulated growth of multiple myeloma cells, inhibits tumor growth, and increases survival in 5T33MM mice (30, 31). A newer version of the 5T33MM model was developed recently that expresses enhanced green fluorescent protein, allowing investigators to trace and quantify the anatomic distribution of multiple myeloma cells as they colonize in bone marrow, lymphoid organs, and visceral tumor sites (21). The refinement and innovations in 5TMM models will allow these to continue as useful preclinical models in testing novel multiple myeloma therapeutic agents.

Xenograft models of human myeloma in mice

In contrast to the mouse multiple myeloma models, the xenograft models of human myeloma tumors or cell lines that

<table>
<thead>
<tr>
<th>Cell line name</th>
<th>Description</th>
<th>Unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>826/5</td>
<td>Standard multiple myeloma line</td>
<td>Obtained from ATCC (10)</td>
</tr>
<tr>
<td>826/Dox6</td>
<td>Multiple myeloma line</td>
<td>Overexpress Pgp drug transporter (15)</td>
</tr>
<tr>
<td>826/MR20</td>
<td>Multiple myeloma line</td>
<td>Overexpress BCRP transporter/reduced Topo II levels (16)</td>
</tr>
<tr>
<td>826/L55</td>
<td>Multiple myeloma line</td>
<td>Increase DNA repair, PA path, NPSH levels (17)</td>
</tr>
<tr>
<td>MM1.S-</td>
<td>Multiple myeloma line</td>
<td>Dexamethasone sensitive (18)</td>
</tr>
<tr>
<td>MM1.R-</td>
<td>Multiple myeloma line</td>
<td>Dexamethasone resistant (18)</td>
</tr>
<tr>
<td>U266</td>
<td>Multiple myeloma line, autocrine signaling</td>
<td>Interleukin-6 dependent (19)</td>
</tr>
<tr>
<td>Transgenic lines</td>
<td>BCL2, BCL-x(L), MCL-1, Puma, Bax</td>
<td>Allow definition of molecular pathways</td>
</tr>
<tr>
<td>Future need</td>
<td>Multiple myeloma lines resistant to novel agents</td>
<td>Velcade and other novel agents</td>
</tr>
</tbody>
</table>

Abbreviations: ATCC, American Type Culture Collection; NPSH, nonprotein sulfhydryl.
are transplanted into SCID-Hu, NOD/SCID, or SCID-Rab mice offer the unique ability to test therapeutics in vivo against human myeloma. The xenograft models include localized disease, from s.c. tumor tissue xenografts, and models that mimic diffuse disease through injection of multiple myeloma cells or cell lines via i.v. injections. The SCID-Hu model enhances our ability to study myeloma development in a human microenvironment and provides a model for reproducible growth of primary myeloma cells and testing of therapeutics (23–25). The advantages are the ability to study human multiple myeloma cell interaction with a human microenvironment and a model that more closely mimics human disease than when cell lines are used (23–25). The disadvantages include difficulty in doing molecular studies, the small size of the tumor and microenvironment, and potential contamination of host cells. A NOD/SCID model where multiple myeloma cells are labeled with green fluorescent protein and then introduced to NOD/SCID mice by i.v. injection creates a model of diffuse multiple myeloma that can be visualized using whole-body, real-time fluorescence imaging to reproducibly quantify tumor burden (32). The model has the advantage of frequent, serial, and noninvasive monitoring and the opportunity to isolate the tumor cells from animals before molecular profiling or drug treatment. The SCID-Rab model avoids the ethical concerns about the use of human fetal bone tissue in the SCID-Hu model and instead uses rabbit bones implanted s.c. in unconditioned SCID mice (33). The SCID-Rab multiple myeloma model allows for successful engraftment of bone marrow cells from multiple myeloma patients or CD138-selected myeloma plasma cells and led to the production of matching M-protein isotypes, and typical myeloma clinical manifestations. The myeloma cells were shown to grow exclusively in the rabbit bone, albeit with the capability to metastasize into remote sites. The SCID-Rab model supports the growth of multiple myeloma cells in a nonmyelomatous, nonhuman, and nonfetal microenvironment. The SCID-Hu, NOD/SCID, and SCID-Rab models offer reliable and reproducible models for testing compounds against human myeloma cells in varying microenvironments.

**Animal studies provide an imperfect model**

Animal models provide systems to rapidly test novel therapeutics in a preclinical setting and the ability to examine pharmacodynamics, test targeted therapeutics to ligands within a particular tumor, and test the ability of an agent to affect a

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**Table 2. In vivo models of multiple myeloma**

<table>
<thead>
<tr>
<th>Model name</th>
<th>Description</th>
<th>Unique features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse myeloma</td>
<td>Myeloma develops from aged mice</td>
<td>Immunocompetent model, maintained by syngeneic transfer to young mice</td>
</tr>
<tr>
<td>STMM Series (21, 22, 28)</td>
<td>ABL-MYC expressed in BCL-x(L) transgenic mice</td>
<td>Unique transgenic model of multiple myeloma</td>
</tr>
<tr>
<td>ABL-MYC in BCL-x(L) (26)</td>
<td>ABL-MYC expressed in BCL-x(L) transgenic mice</td>
<td></td>
</tr>
<tr>
<td>Xenograft human models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCID-Hu (23–25)</td>
<td>Immunoincompetent model, transplant with human primary cells or cell lines</td>
<td>In vivo human microenvironment</td>
</tr>
<tr>
<td>NOD/SCID (27)</td>
<td>Immunoincompetent model, transplant with human primary cells or cell lines</td>
<td>Unique visualization using green fluorescent protein - tagged cells</td>
</tr>
<tr>
<td>SCID-Rab (33)</td>
<td>Immunoincompetent model, transplant with human primary cells or cell lines</td>
<td>Uses rabbit bone, avoids need for human fetal bone tissue</td>
</tr>
</tbody>
</table>

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**Table 3. Select characteristics comparing mouse models with human multiple myeloma**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mouse STMM</th>
<th>HU-XENO Subcutaneous</th>
<th>HU-XENO i.v. Injection</th>
<th>Human multiple myeloma patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous age-related origin</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Bone marrow involvement</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Osteolytic bone lesion</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Induction of angiogenesis</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tumor mass related M-protein</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Biological</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vitro stroma dependency</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Interleukin-6 and insulin-like growth factor-I as growth factors</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Adhesion molecule phenotype: CD11a, CD44, CD29</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>In vitro angiogenesis induction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>In vitro migration and invasion</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Expression of matrix metalloproteinase-9</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
specific molecular target. Multiple myeloma cell lines offer the advantage of rapid disease without the latency period of primary tumor cells, although they disproportionately represent aggressive, advanced multiple myeloma tumors. Table 3 compares some of the clinical and biological characteristics shared, or not, between the animal models and human multiple myeloma. Induction of angiogenesis and tumor mass-related M-protein is observed in most multiple myeloma patients and in the mouse myeloma model and xenograft multiple myeloma models. However, dissimilarities exist, including whether the bone marrow is involved or whether migration and invasion are observed.

The panel discussed the time points and biological targets that could be tested in the various systems. Should agents be delivered at the time of injection of tumor cells or on confirmation of tumor establishment? For example, the 5TMM models provide a system to test compounds aimed at blocking the bone marrow homing of multiple myeloma cells, whereas the SCID-Hu model with primary multiple myeloma cells provides the ability to test agents targeted at the microenvironment (34). In addition, multiple myeloma cells with fluorescent tags provide unique systems for visualizing cells in living animals and a more complete description of cell localization in pathology studies than unlabeled cells. The panel noted the value of models that use multiple myeloma cells that have never been exposed to culture medium, serum or plastic.

The panel urged caution when using the various animal models discussed, as each has their limitations for preclinical validation of therapeutic strategies. It is important to plan for what measures will be used to show success. Studies should show decreased tumor burden, reduction of M-protein levels, or increased survival. However, caution should be used to rule out therapeutic strategies simply because they do not work in animal models. Future investigations need to carefully consider the weaknesses of each model and the needs for new, lasting treatments for patients and balance with the responses deemed necessary in animal models before it is acceptable to translate into myeloma patient trials.

How to Apply Model Systems for Validating Drug Combinations

The advance of new treatments for multiple myeloma, with many agents targeting specific molecules or molecular pathways, calls for the combination of therapies to enhance cytotoxicity, avoid development of drug resistance, and in some instances, allow for lower doses (35, 36). Successful combinations for treating some cancers, including resistant cancers, have emerged through rational, logical thought, whereas others emerge through serendipity. Two HTS systems were discussed that can be applied to testing combination therapy (37–39). These provide rapid methods for identifying lead compounds and anticancer drugs either for chemical probes to study a particular target or as drug candidates. HTS used in conjunction with validated cell models allows for the identification of small molecules that is not limited by the current knowledge necessary for traditional structure-based drug design. Once a hit is identified, the agent can be further refined using structure-based approaches. Leading academic groups have made discoveries of new agents, including CucQ (JSI-124), the highly selective Janus-activated kinase/signal transducer and activator of transcription 3 inhibitor, and tubacin, an inhibitor of HDAC6. Both of these molecules are in preclinical development and should enter human myeloma trials this year. Several academic centers are developing HTS and will play new roles in drug development and form partnerships with the pharmaceutical and biotechnology industry. Increasingly, novel chemical entities can be identified, screened in in vitro and in vivo systems at academic institutions, and then licensed to industry partners for further pharmacokinetic and pharmacodynamic studies. The approach is likely to greatly increase the number of therapeutics under development for multiple myeloma and increase the need for prioritization and standardization in preclinical and clinical testing.

The novel agents generated through HTS provide examples of the many novel compounds designed against specific molecular targets relevant for multiple myeloma. Knowledge of the pathways targeted allows for the rational design of
combinatorial therapies. An example is the combination of the HDAC6 inhibitor tubacin with the proteasome inhibitor bortezomib (40). The proposed mechanism for this combination is that unfolded or misfolded ubiquitinated proteins are degraded by both proteasomes and aggresomes. Aggresomes are dependent on HDAC6 activity. By targeting both pathways, an increase in the accumulation of ubiquitinated proteins is expected and thus significant cell stress and cytotoxicity in multiple myeloma cells.

An additional example of combination therapy under development is the proteasome inhibitor bortezomib with inhibitors of the protein chaperone, Hsp90. Hsp90 has a role of stabilizing and refolding unfolded proteins. Inhibition of this capacity in multiple myeloma cells, combined with reduced proteasome degradation of misfolded proteins, should lead to increased cell stress and cytotoxicity. One inhibitor of Hsp90, 17-allylamino-17-demethoxygeldanamycin, is highly insoluble and therefore is undergoing evaluation in cremophore, (KOS 953) both alone and in combination with bortezomib. Novel, water-soluble, Hsp90 inhibitors are being developed, such as IPI-504 from Infinity Pharmaceuticals (Cambridge, MA), both for testing alone and in combination with the proteasome inhibitor bortezomib.

It is necessary to integrate pharmacology and in vitro models in drug development for multiple myeloma. The choice of assay systems is especially important for identifying novel small-molecule inhibitors through HTS. The animal models and experimental design for combinatorial therapy need to be well thought out so as to not give misleading or inaccurate data that could stall the development of potentially useful compounds for treatment of multiple myeloma.

Summary and Future Directions

Multiple myeloma research benefits, compared with other cancers, from having ~60 cell lines derived from patients that serve as in vitro models of the disease. However, most of these are derived from patients with late-stage, aggressive, drug-resistant multiple myeloma and do not represent the heterogeneity of the disease. Assays need to be developed to create new multiple myeloma cell lines from newly diagnosed patients and patients with early disease. These new models will allow investigators to gain insight into the mechanisms of how resistance develops. Assays, which use primary patient samples without exposing them to culture systems, plastic or serum, need to be refined and further developed. Finally, cell studies that model drug resistance need to be exploited when testing new agents or combinations of agents.

Many animal models of multiple myeloma aid in the preclinical development of new therapeutics. Each of the models has its own strengths, caveats, and weaknesses. The models vary in ability to test therapeutics before detectable disease or at onset of overt disease, in the means by which tumor burden can be assessed, and the ability to do timely experiments avoiding long latency periods. The models further vary in ability to test different biocompartments, such as within bone lesions or the s.c. space. Investigators need to choose models and experimental design in an appropriate manner, understanding the caveats, and use caution when interpreting positive or negative results. M-protein levels do not always reflect an accurate measure of tumor burden, especially when using aggressive cell line clones.

Existing models need to be exploited in an attempt to define and characterize multiple myeloma stem cells. Standard methods used in other stem cell studies, such as tagging and phenotypic analysis, need to be tested. Methods for reproducibly and reliably isolating putative multiple myeloma stem cells need to be refined and further developed (43, 44). New models need to be created that allow for identification of stem cells at various stages of disease. For example, clonogenic studies could be done on drug-resistant tumors that may isolate nonresistant underlying stem cells.

An array of additional animal models would provide valuable resources in multiple myeloma research. New models should be created that are designed for testing combinations of therapeutics. Models could be developed from patients who relapse from therapy. Animal models should be developed to aid in pharmacologic testing of novel compounds. Current models do not replicate human toxicity and side effects but are sufficient for assessing effect on tumor burden. In summary, models need to be used to help set priorities for translation of new treatments into phase I and phase II clinical trials and for testing combinations of new and existing agents.

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