Meeting report: The future of preclinical mouse models in melanoma treatment is now

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On October 17th, 2012 a group of 28 basic researchers and physician scientists met at the Wistar Institute in Philadelphia, PA to initiate detailed discussions on the current status and future prospects of preclinical studies in human melanoma, focusing on the mouse as an experimental system. The goal of this meeting, organized by Drs. Glenn Merlino (NCI), Terry Van Dyke (NCI) and Meenhard Herlyn (Wistar), was to facilitate the development of better preclinical melanoma models by giving oncologists the opportunity to tell modelers what information they need in order to improve clinical trials, and to have modelers acquaint clinicians with the preclinical state-of-the-art. Participating physician scientists included Drs. Marcus Bosenberg (Yale University), Keith Flaherty (Massachusetts General Hospital), Lynn Schuchter (University of Pennsylvania), David Solit (Memorial Sloan Kettering), Suzanne Topalian (Johns Hopkins University), Clemens Krepler (Wistar Institute), and Nicolas Acquavella (NCI). In addition to the organizers, participating basic researchers included Drs. Andrew Aplin (Thomas Jefferson University), Sheri Holmen ( Huntsman Cancer Institute), Martin McMahon (University of California at San Francisco), and Keiran Smalley (Moffitt Cancer Center). Other notable attendees included Drs. Ken Fasman (Vice President and CSO, Adelson Medical Research Foundation), Alison Martin (CMO, Melanoma Research Foundation Breakthrough Consortium), and Wendy Selig (President and CEO, Melanoma Research Alliance).

An underlying premise of the Wistar meeting was that no clinical trial should be conducted without a solid rationale derived from rigorous preclinical studies in hypothesis-predictive models. Unfortunately, clinical trials always seem to be one step ahead of thorough preclinical studies that should be used to support them. Preclinical testing of anti-cancer drugs currently employs an approach in which efficacy endpoints are determined by the growth responses of established human melanoma cell lines after subcutaneously engraftment into immune-compromised mice (cell line xenografts). Such models are overly reliant on cell lines that have been altered through adaptation to growth on plastic and in an ectopic microenvironment that lacks an immune system. As a consequence cell line xenograft models have in general proven to be poorly predictive of clinical outcome, and most drugs fail in clinical trials. As with other cancers, the melanoma field is in dire need of improved preclinical models that are more predictive of clinical response. This is particularly the case now that some success has been achieved in the clinic with a targeted therapeutic that significantly extends lives of certain melanoma patients. The glimmer of hope that has been rendered, however, has also underscored the reality that aggressive cancers ultimately become resistant to single agent therapies. This report will review meeting highlights, including discussions on the current state of melanoma therapy, on promising mouse melanoma models, and how these two rapidly advancing fields can best be integrated into improved clinical care. We also provide a description of new approaches that could facilitate preclinical therapeutic evaluation, and recount discussions and conclusions concerning immediate clinical priorities, and future prospects and challenges.

Clinical update and perspective

Drs. Flaherty and Topalian began the meeting by bringing the audience up-to-date on the status of targeted and immune-based melanoma therapies. The traditional standard of care for advanced melanoma, for many years consisting of chemotherapeutic agents such as dacarbazine and/or immunotherapy with interleukin-2 (IL-2) or interferon-α, was very limited, demonstrating short-lived (<6 months) responses in 10–20% of patients. Significant progress has now been made by focusing on the molecular disease subgroups, as delineated by their apparent ‘driver’ oncogenes. A driver oncogene can be defined based on the consequences of its inhibition: direct targeting of the oncogene product would result in a single-agent anti-tumor effect of regression or stasis. For nearly 50% of patients BRAFV600E plays this role and inhibiting mutant BRAF function (e.g., with vemurafenib or dabrafenib) or simultaneously inhibiting both BRAF and...
MEK (e.g., by including trametinib) in metastatic melanoma significantly improves survival time. However, the extensive heterogeneity in tumor response among individual patients remains a challenge. In an additional non-overlapping 20% of patient cancers mutant NRAS is the driver, but the inability to as-of-yet directly target NRAS has forced the employment of indirect targeting strategies, such as interfering with NRAS regulators or downstream effectors. In this regard, single-agent inhibition of downstream MEK has a potential role in quelling melanomas. However, a significant number of patients receive no benefit from this treatment, and for those who do the responses are of less magnitude or duration compared to BRAF-mutant melanomas treated with BRAF inhibitors. c-KIT mutations appear to be likely drivers in about 1% of melanoma patients (and higher in acral and mucosal melanomas), but the mutations are more widely distributed over the coding region and not entirely aligned with available c-KIT inhibitors with regard to molecular or clinical susceptibility. GNAQ or GNA11 mutations are the drivers in no more than 1% of all cutaneous melanoma cases (but 80–90% of uveal melanoma cases). Unfortunately, as with NRAS, indirect strategies currently appear to be the only tractable approach for this class. Notably, in nearly 30% of all melanoma cases the driver oncogene, assuming that there is a single major driver, has not yet been identified. Experimental model systems will be needed to determine which, if any, of the recently identified melanoma oncogenes could play this role, such as RAC1, GRIN2A, ERBB4, or other MAPK drivers. Interestingly, this melanoma subset also contains a disproportionate number of NF1 nonsense mutations.

The most successful future anti-melanoma therapies will very likely consist of combinations of drugs that individually have only modest or transient clinical activities. The most efficacious molecularly-targeted combination therapy to date, a BRAF inhibitor plus a MEK inhibitor in BRAF inhibitor-naive patients whose tumor harbors a BRAF mutation, is associated with a 10% complete response rate, a 75% objective response rate, median progression-free survival of 9–10 months, and a 1-yr survival rate of 80%. While these results are exciting compared to the picture only 5 yr ago when no effective targeted treatment was available, there is a clear need for further advances in this molecular subtype, and the others remain largely refractory to treatment. For NRAS-mutant melanoma, the best reported outcome with a single-agent MEK inhibitor is no complete responses, 20% objective response rate, and median progression-free survival of 4 months. For c-KIT mutant melanoma the response rate to imatinib, which targets c-KIT and some other tyrosine kinases, is 10–20% with median progression-free survival of 4 months.

Melanoma has historically been viewed as an immune-responsive disease, although early immunotherapeutic approaches, such as treatment with interferon-α or IL-2, demonstrated limited success and were associated with significant toxicity. However, the use of adoptive transfer of tumor-infiltrating lymphocytes has been encouraging and results in durable complete responses in some metastatic melanoma patients. The value of immune-based approaches has been further validated by the recent development and early success of immunomodulatory agents that enhance the effector arm of the immune system by targeting inhibitory factors. These strategies rejuvenate anti-tumor T cell functions by blocking immunologic checkpoints, negative regulators of the immune system, which can thwart normal anti-tumor mechanisms. In particular, treatments with monoclonal antibodies that block either cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 receptor (PD-1), or PD-1 ligands (PD-L1 and PD-L2) have shown promise in the clinic, although only a subset of melanoma patients responds. Drugs targeting CTLA-4 (e.g., ipilimumab) have demonstrated an objective response rate of approximately 10% and durable disease control in approximately 20% of patients with advanced melanoma, while those inhibiting the PD-1 or PD-L1 (e.g., nivolumab or BMS-936559) induce objective responses in approximately 30% or 20% of patients, respectively. Emphasis is currently being placed on identifying biomarkers that will predict which patients will respond best to these immunotherapeutic agents. Melanoma oncologists are particularly excited about ongoing trials employing combinations of immunomodulatory drugs, or immunomodulatory plus molecularly targeted therapies, which may increase response rates based on preclinical models.

The melanoma field is currently confronted with a ‘challenge of riches’ because the pharmaceutical industry is eager to test each new generation of signaling inhibitors in melanoma patients. Unfortunately, sorting out the different inhibitors in patients as to which is most optimal or which target is the most effective with the least side effects will take years and tens of millions of dollars in costs for large clinical trials. Much drug comparison could and should therefore be performed first in preclinical models, which could also be front-line in assessing whether combination drugs should be given at the same time or in sequence and with what frequency. Based on preclinical data already generated using immortalized human melanoma cell lines in vitro and/or transplanted into immunodeficient mice, a number of therapeutic strategies appear to be justifiable in genetically defined patient subpopulations (see Table 1). However, major concerns with regard to the promise of various drugs and treatment strategies for clinical translation remain. (1) Are current preclinical data sufficiently predictive of patient outcomes to support clinical trials? (2) How can patients be optimally selected for each treatment? (3) How can likely resistance mechanisms be anticipated? Given the range of therapeutic possibilities envisioned, overcoming the significant barriers between promising theoretical or nascent experimental predictions and improved patient care will require significant
improvement in the accuracy of preclinical predictors. There were extensive discussions at this meeting focused on improved melanoma modeling approaches in mice that are based on cutting-edge technologies in genetic and biological engineering, and how they may provide an avenue for achieving such capabilities.

**Preclinical update and perspective**

The melanoma field now finds itself with multiple promising model systems for preclinical testing. As described below, these include human and mouse melanoma cell lines, patient-derived xenograft (PDX) models, genetically engineered mouse (GEM) models, and GEM-derived allograft (GDA) models. All of these systems have strengths and weaknesses, and all need to be further validated with respect to their value for preclinical efficacy and biomarker evaluation for human studies. Drs. Krepler, Bosenberg, McMahon, Acquavella, Holmen and Merlino discussed many of the current models.

Established human and mouse melanoma cell lines continue to be workhorses for mechanistic studies. Subjecting such lines to drug selection schemes can yield useful information about how cancer cells become resistant to that particular drug, as exemplified in Dr. Solit’s work on identifying mechanisms of acquired resistance to BRAFV600E inhibition associated with aberrant RNA splicing. However, a limitation of in vitro culture is that established cell lines become inexorably altered in the process, thereby limiting their ability to predict drug clinical activity. Hence, more recent studies have been using human melanoma cell cultures with only limited passage in vitro.

Subcutaneous transplants of fresh tumor tissue into immunocompromised mice, the PDX models, have become particularly attractive for use in therapeutic evaluation because they avoid cell culture altogether. Dr. Herlyn’s lab has successfully established a program in which over 140 PDXs from a wide spectrum of melanoma tissues have been generated and banked, including from patients who have relapsed after BRAF or BRAF/MEK inhibitor therapy. In this approach tumor samples are collected under IRB approval as fresh biopsy tissue or fine needle aspirate. Within hours tumor chunks, aspirates or purified cell suspensions are implanted subcutaneously in NOD scid IL-2 receptor gamma chain knockout (NSG) mice, which lack a functional immune system. The transplanted tissue or cells, even in very small numbers and irrespective of stage, mutational background, and time in cryogenic storage, reliably form a tumor graft in permissible mice, such as the NSG strain. Melanoma PDXs have a take rate of about 90%, and can be expanded over 3 mouse passages and stored as a live tumor bank. In drug efficacy evaluation, PDX mice are continuously treated with appropriate inhibitors to maintain conditions similar to those used for patients.

Our ability to choose optimal second line single or combination agents is highly dependent on our understanding of the biological signatures of melanomas with intrinsic or acquired resistance to first line agents such as kinase inhibitors. Libraries of PDX models are expected to facilitate these analyses, allowing for general efficacy prediction and identification of biomarkers reflective of drug responses. Notably, a single PDX can also be employed in real time to help the patient from whom it was derived. By creating avatars of a patient’s melanoma that has relapsed on current therapies or clinical trial protocols, ‘mini human-in-mouse trials’ or ‘co-clinical trials’ can be conducted to facilitate the selection of effective drugs, drug combinations and dosing regimens for that specific patient. The often-rapid progression of stage IV melanoma patients makes this personal cancer-directed approach a challenging goal; however, as novel

### Table 1. Proposed drug and drug combination treatments for melanoma molecular subtypes

<table>
<thead>
<tr>
<th>Molecular Subtype</th>
<th>Drug Combinations</th>
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| BRAF mutant melanoma | - Intermittent administration of BRAF inhibitor  
- Combination of BRAFi with CDK4 inhibitor  
- Combination of BRAFi with PI3K/AKT/mTOR inhibitor  
- Combination of BRAFi with mdm2 antagonist in p53 wt tumors  
- Combination of BRAFi with HGF/MET inhibitors  
- Combination of BRAFi with DHODH inhibitors  
- Combination of BRAFi with anti-VEGF antibodies  
- Combination of BRAFi T cell-directed immune therapies CTLA-4 inhibitor; PD-1/PD-L1 inhibitor; IL-2; adoptive cell transfer immunotherapy |
| NRAS mutant melanoma | - Combination of MEK inhibitor with CDK4 inhibitor  
- Combination of MEK inhibitor with mdm2 antagonist in p53 wt |
| GNAQ/GNA11 mutant melanoma | - PKC inhibitor  
- Combination of MEK inhibitor with PI3K/AKT/mTOR inhibitors |

For treatment of patients with BRAF mutant melanoma, all drug combinations with BRAFi could also include inhibitors of MEK, which are currently being used in the clinic.
therapies induce longer remissions and targeted and immunotherapies move to adjuvant settings, such a goal may soon be realized. The PDX model may represent a significant improvement in the ability to more accurately predict clinical activity, and the ongoing work in the Herlyn lab and those of others represent critical efforts toward validating and optimizing this important outcome. However, as with all model systems, the PDXs have limitations, most notably the required use of immunocompromised mice.

Dr. Acquavella led a discussion on the importance of a functional immune system, which will be required to effectively study the promising class of immunomodulatory therapies in melanoma, especially in combination with kinase inhibitors as a novel application. A tumor exhibiting intrinsic immunogenicity on an immunocompetent host would result in the intratumoral recruitment of cellular elements comprising both the innate and adaptive arms of the host immune system. This desired attribute could recapitulate the failure of host immunologic barriers to impede effective antitumor responses in humans. Moreover, the presence of tumor infiltrating lymphocytes in immunocompetent mouse models would recapitulate the occurrence of functionally tolerant T-cell repertoires against unknown tumor antigens in patients with melanoma. A point of concern is the insertion of artificial genetic information (e.g., ‘non-self’ proteins) into tumors that may inadvertently increase their immunogenicity. The artificial aspects of this sort of immunity may not translate well into human clinical trials, thus compromising the clinical predictive value of the model. Therefore, modeling strategies that circumvent this approach should be prioritized. The major challenge for tumor immunologists is to identify which tumor antigens (e.g., self-antigens, products of mutated genes, cancer testis antigens) are most likely to mediate a successful anti-tumor response. Preclinical modeling of both ‘self’ and ‘non-self’ antigen reactivity is essential for the development of novel immunotherapies. Development of antigenic systems targeting the products of mutated oncogenes and tumor-suppressor genes may serve as definite proof that these epitopes could mediate potent T-cell antitumor responses. This conundrum illustrates the importance of faithfully evaluating antigen-specific immunity and reaching accurate conclusions to appropriately guide the design of clinical trials.

Ideally, human tumor graft models should also include a transplanted functioning human immune system. While this achievement is possible, the technology is immature, tedious and expensive. A functional human immune system can be generated by introducing human CD34+ hematopoietic stem cells into mice previously subjected to gamma irradiation-induced myeloablation. However, unless or until such humanized mice can be produced rapidly in the required numbers, GEM models provide the only alternative to immune therapy assessment. These models may also be required for ‘filtering’ agents to be tested in the relatively limited PDX resource.

As discussed by Drs. Bosenberg and Merlino, mice rarely spontaneously develop melanoma, but can be genetically engineered to do so by activating oncogenes relevant to human melanoma, such as mutant BRAF or mutant NRAS, and/or via inactivation of key tumor suppressors, including CDKN2A or PTEN. A deeper molecular understanding of melanoma along with recent technological advances (e.g., inducible Cre-based recombination and tet-inducible transgene expression) have led to the engineering of mouse models that develop de novo melanomas with many characteristics of the human disease. For example, expression of the hepatocyte growth factor/scatter factor ligand for the MET receptor allows melanocytes to survive outside of the hair follicles, where they typically reside in mouse skin, to the epidermal-dermal junction and the epidermis, where most reside in human skin. Ultraviolet radiation, thought to play a role in the etiology of 80% of human melanomas, has also been incorporated into many model systems. In short, if appropriately developed, GEM models offer the best opportunity to incorporate relevant genetic, biological and etiological factors to recapitulate the natural history of melanomagenesis, including tumor heterogeneity and genomic instability – two complex and challenging phenotypes. An understanding of mechanisms responsible for the differential therapeutic responses observed among individual patients would represent a boon to both preventive and interventional clinical practice. Importantly, employing GEMS directly as preclinical models allows an analysis of incipient melanoma in the context of a functional immune system.

Dr. Holmen is using a new approach to melanoma modeling, the RCAS/TVA system. In these models, transgenic mice expressing the avian retroviral receptor, TVA, under the control of a melanocyte-specific promoter are susceptible to infection by avian leukosis virus-based retroviral vectors encoding relevant melanoma oncogenes. Infection results in stable integration of the virus into the genome of replicating cells, allowing for long-term expression. The major advantage of these models is that they can be used to evaluate multiple genes implicated in melanomagenesis, either alone or in combination. The RCAS/TVA system, as with inducible GEM systems, also permits temporal and spatial control of gene expression, which facilitates tumor progression and maintenance studies. Tumors evolve from gene mutations in developmentally normal cells in the context of an unaltered microenvironment, which closely mimics the context of human disease. Some advantages of GEM models can create disadvantages for preclinical studies. In the best models tumors arise de novo and therefore, like the human disease, are less predictable. Furthermore, primary tumors often develop robustly at multiple sites. These features are problematic for designing preclinical studies,
particularly metastatic disease studies. A compromise approach that retains many advantages uses GEM-derived allografts. Here, de novo mouse melanomas engineered to mimic the genomic and environmental lesions associated with their human counterparts are harvested and expanded by serial orthotopic transplantation in immunocompetent mice. GDAs combine the tractability for feasible, high-quality drug studies (as with PDX models) with the validity of maintaining compatible tumor-host interactions, including a fully functional immune system (as with de novo GEM models). Moreover, while products of genetically engineered driver oncogenes are tolerized in GEMs, they can be immunogenic in GDA host mice, which is more relevant to the immune environment of human cancer. GDAs are especially amenable to the study of metastatic disease. Considering actual responses of metastatic tumors instead of primary tumor growth retardation may help narrow the existing ‘bench to bedside’ translational gap. GDAs and GEMs are both invaluable for evaluating immunotherapies and drugs that affect the immune system. Indeed, since the immune system is likely to play a role in the overall response to any given therapy, the presence of the cognate immune system for any model may be paramount in developing accurate human response hypotheses.

Complexity in models and underdeveloped preclinical approaches hinder progress

As is clear from the above summary, the need to faithfully model the complexities of human cancers for deriving meaningful therapeutic response and biomarker discoveries also limits the feasibility for broad usability of the most accurate mouse models in preclinical evaluation. Although the development of standard preclinical systems and associated approaches is in its infancy, a significant number of studies indicate that the above-described model systems can provide guidance for productive human research outcomes. Several studies have indicated the possibility of identifying biomarker signatures of disease and treatment responses, and have reported therapeutic outcomes similar to those observed in the clinic. The ultimate goal is to generate hypotheses predictive of human outcomes so as to design clinical trials with increased probability of developing effective clinical management strategies while reducing unexpected adverse effects in human studies. Notably, preclinical therapeutic evaluation in a GEM model of pancreatic islet cell carcinoma by Dr. Doug Hanahan recently led to a phase III study and approved therapy for multiple endocrine neoplasia. Despite this groundbreaking study, however, few labs have the range of expertise required to perform such integrated translational studies, and significant development of preclinical protocols with a range of models is needed. Several academic initiatives have been launched to internally expand preclinical studies using PDX models, GEM models or derivative approaches; as such studies mature, results will guide the development of effective preclinical protocols.

The NCI Center for Advanced Preclinical Research

A unique operating principle has been established by the Center for Advanced Preclinical Research (CAPR) at the Frederick National Laboratories for Cancer Research under the purview of the NCI. CAPR partners with clinical, translational and basic scientists in the public and private sectors to perform integrated therapeutic and biomarker studies using complex mouse models adapted for optimized preclinical evaluation. Dr. Van Dyke, CAPR director, described the Center, its operating principles and expertise, and how it might partner with the melanoma research community to accelerate translatable studies to the clinic. CAPR is designed to provide a bridge between basic discovery and applied cancer research in both intramural and extramural communities. It is staffed on a contractual basis from the Scientific Applications International Corporation (SAIC), and has all relevant expertise and technologies to move basic discovery into preclinical assessment at a scale that will inform clinical trial design. Thus, CAPR provides basic and clinical scientists with access to preclinical assessment of potential therapeutics, biomarkers, and novel therapeutic targets while developing ‘best practices’ for preclinical predictability of human studies without draining resources central to the basic and clinical efforts themselves. CAPR proficiencies include: (1) biomarker/molecular signature assessment of disease stages and therapeutic responses, (2) hypothesis generation for clinical research based on systems responses to therapeutics, (3) preclinical evaluation of combinatorial therapies, (4) comparative assessment of predictive power among models (PDX vs. GEM vs. GDA models), (5) technology development to overcome barriers to scale-up and throughput, (6) development and application of clinically relevant therapeutic endpoints (e.g., molecular imaging), (7) therapeutic target discovery and validation using predictive preclinical cancer models, and (8) development of novel engineering strategies, retooling of established models for preclinical research, and establishment of new models for unmet needs.

The Center for Advanced Preclinical Research achieves its mission to develop an efficient and predictive preclinical arena through internal projects focused on applied preclinical development and via extensive collaborative partnerships (both private and public) focused on therapeutic and biomarker development. Partnering organizations include pharmaceutical, biotechnology and computational science companies, foundations, and public clinical and basic research institutions (including both
We coordinate our activities, including with pharma, the moving from a lead compound to a ‘real’ drug. The better inhibitors need to come not just from pharma but also validation in experimental models. In addition, novel wealth of potential new targets that will all require novel advances were achieved independently with two very different approaches: first, through the immune system, either by adoptively transferring the patient’s own activated tumor infiltrating lymphocytes or by blocking negative regulatory molecules on lymphocytes; and second, by blocking signaling molecules with small molecule inhibitors. While strategies for the very next clinical trials appear obvious from a wealth of existing clinical and preclinical data (see Table 1), the future in melanoma therapy beyond the next 2 yr is less clear, particularly in signaling therapy. To accelerate and increase success, guidance for the best future targets and therapies have to come from preclinical studies utilizing multiple models that synergize to mimic the clinical pathologies and challenges, rather than a single model approach. We need to achieve a high level of coordination between experimentalists and clinicians to ensure that the most appropriate models are used for each disease sub-group. Genetic signatures of melanomas have been helping to guide strategies for therapy. Now genome-wide screens are providing us with a wealth of potential new targets that will all require validation in experimental models. In addition, novel inhibitors need to come not just from pharma but also from academia as many obstacles are faced when moving from a lead compound to a ‘real’ drug. The better we coordinate our activities, including with pharma, the faster we can move forward. The recent creation of CAPR could be a real boost for the field, but we need to find the funding to support these integrated studies, a major challenge in the current climate of tight budgets. On the clinical side, consortia established by the NIH can be extended for more flexibility and speed by independent ‘honest brokers’ such as the Breakthrough Consortium of the Melanoma Research Foundation.

Melanoma is a complex disease and genetic events are only one aspect in understanding the disease and in developing new therapeutic strategies. We need to develop biological signatures that encompass the many epigenetic events and microenvironment signals so critical in these diseases. No single laboratory can cope with the multitude of challenges. Instead, we need to develop platforms for communication and exchange of data and models in order to continue the rapid progress of the last few years. A consortium-type platform with regular meetings and a Steering Committee for coordination should bring the clinical and experimental investigators together. Curing the many forms of melanoma is our challenge and our mission. Only by working together can we achieve our lofty but vital goal.

Meeting conclusions

Melanoma therapy has progressed in the last 3 yr at an unprecedented pace culminating in true benefits for patients not just for stabilizing the disease and prolonged progression-free survival but also for overall survival. The advances were achieved independently with two very different approaches: first, through the immune system, either by adoptively transferring the patient’s own activated tumor infiltrating lymphocytes or by blocking negative regulatory molecules on lymphocytes; and second, by blocking signaling molecules with small molecule inhibitors. While strategies for the very next clinical trials appear obvious from a wealth of existing clinical and preclinical data (see Table 1), the future in melanoma therapy beyond the next 2 yr is less clear, particularly in signaling therapy. To accelerate and increase success, guidance for the best future targets and therapies have to come from preclinical studies utilizing multiple models that synergize to mimic the clinical pathologies and challenges, rather than a single model approach. We need to achieve a high level of coordination between experimentalists and clinicians to ensure that the most appropriate models are used for each disease sub-group. Genetic signatures of melanomas have been helping to guide strategies for therapy. Now genome-wide screens are providing us with a wealth of potential new targets that will all require validation in experimental models. In addition, novel inhibitors need to come not just from pharma but also from academia as many obstacles are faced when moving from a lead compound to a ‘real’ drug. The better we coordinate our activities, including with pharma, the faster we can move forward. The recent creation of CAPR could be a real boost for the field, but we need to find the funding to support these integrated studies, a major challenge in the current climate of tight budgets. On the clinical side, consortia established by the NIH can be extended for more flexibility and speed by independent ‘honest brokers’ such as the Breakthrough Consortium of the Melanoma Research Foundation.

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Recommendations

1. Immediate clinical priorities
   - Explain the heterogeneity of melanoma patient response to targeted therapy (in both scale and duration).
   - Identify mechanisms of primary (intrinsic) and secondary (acquired) resistance to targeted therapies.
   - Explain why only some patients respond to immunologics and achieve durable responses.
   - Identify patient cohorts that will initially respond to a specific immunotherapy.
   - Identify patient cohorts that will likely experience untoward side effects/toxicity.
   - Identify optimal combination therapies and sequences (e.g., targeted, targeted plus immunotherapy, vaccine plus immunotherapy) and establish optimal sequence of combinations.
   - Identify new targets/therapies for use when current drug trials plateau next year.

2. Longer-term goals
   - Generate tractable preclinical models that recapitulate melanoma evolving in a clinically relevant context.
   - Define the optimal predictive range/relevance of each particular preclinical model.
   - Standardize preclinical studies to allow comparison among models and studies.
   - Establish a Steering Committee of clinicians and modelers to guide preclinical studies and coordinate collaborations with pharmaceutical companies.
3 Current and future challenges

- Modeling heterogeneity and resistance in tumor response to targeted and immune-based therapies.
- Identifying biomarkers of therapeutic response/resistance.
- Modeling genomic instability in mouse melanoma models.
- Humanizing the mouse to allow use of human melanoma in relatively immunocompetent mice.
- Understanding the role of metabolism in mouse and human melanomas.

- Streamlining the search for new effective agents to replenish the limited pipeline and requests for new compounds for preclinical/clinical studies.
- Streamlining functional analyses of candidate targets from genomic studies.
- Availability and cost of adequate amounts of therapeutics for preclinical studies.
- Combining the use of compounds from different pharmaceutical companies.