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The State of Melanoma: Challenges and Opportunities

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Abstract

The Melanoma Research Foundation (MRF) has charted a comprehensive assessment of the current state of melanoma research and care. Intensive discussions among members of the MRF Scientific Advisory Council and Breakthrough Consortium, a group that included clinicians and scientists, focused on four thematic areas—diagnosis/early detection, prevention, tumor cell dormancy (including metastasis) and therapy (response and resistance). These discussions extended over the course of 2015 and culminated at the Society of Melanoma Research 2015 International Congress in November. Each of the four groups has outlined their thoughts per the current status, challenges and opportunities in the four respective areas. The current state and immediate and long-term needs of the melanoma field, from basic research to clinical management, are presented in the following report.

Prologue

The field of melanoma—both research and clinical management—has exponentially expanded over the past decade and has become a paradigm for understanding cancer signaling, tumor immunology and their clinical application. Recognizing how rewired signaling underlies melanoma progression has prompted development of specific drugs (such as vemurafenib and dabrafenib) that decrease tumor burden, although only for a limited time period. Combination drug therapy has also emerged as a way to provide a more sustainable response, raising critical questions relevant to which combination(s) are most effective. In addition, the discovery of processes underlying melanomagenesis, and on mechanisms that underlie the traditional immune suppressive features of advanced melanomas has led to radical progress in devising and applying immune checkpoint therapies. Advances made with melanoma are now being productively applied to other forms of cancer. Yet, despite all of these advances, fundamental questions pertaining to prevention, detection, diagnosis, tumor progression (including dormancy and metastasis) and response to therapy (including resistance) remain: Can we develop better tools to detect melanoma earlier? Will identification of melanoma subtypes dictate therapy? What causes melanoma cells to remain dormant for years and then re-awaken? How does resistance to therapy and metastatic propensity arise so readily, and how does tumor heterogeneity confound efforts to achieve durable responses? Can better tools be developed to prevent and detect metastasis?

What should be the mode and sequence of therapy administration when combinations are used? How do we prioritize the development of immunotherapy-based combinations? How do we select patients for single agent versus combination immunotherapy? What are the mechanisms of resistance to immunotherapy? These questions are of concern to clinicians and basic researchers alike, and many are addressed in the following report.

Prevention

Melanoma arises through progressive accumulation of genetic and (epi)genetic alterations that disrupt homeostatic pathways, resulting in uncontrolled tumor cell proliferation followed by invasion and lymphatic or hematogenous dissemination of the tumor cells to distant sites. In cutaneous melanocytic neoplasms, UV radiation is the primary cause of mutations on sun-exposed skin. Therefore, an individual's susceptibility to melanoma is likely determined by genetic and epigenetic factors that determine the rate at which mutations are generated and fixed (e.g. the intrinsic ability of melanocytic cells to mount shielding responses to UV radiation, for example, by inducing tanning). DNA repair capacity, as well as environmental factors, mainly dose and timing of UV exposure during early periods of life, also dictates risk factors for malignant transformation.

The precise role of UV radiation in carcinogenesis still requires greater understanding, such as the relative contributions of UVA versus UVB wavelengths. This would be of enormous importance, given the ongoing efforts to devise broad-spectrum sunscreen agents approved by the FDA. There is strong evidence for UV-independent mutagenesis in melanoma, a possibility suggested by the occurrence of melanomas at cutaneous locations that are not sun exposed, as well as in the eye and in mucous membranes. Analysis of animal models also shows that melanin, in particular pheomelanin, the predominant pigment present in red-haired/light-skinned individuals, can harbor carcinogenic activity. These observations suggest that the relative degree and type of pigmentation is key in determining melanoma susceptibility. Research of mechanisms that explain the nature of these carcinogenic activities is important and could reveal strategies to neutralize them in the presence or absence of UV irradiation.

Previous studies established a positive correlation between melanoma development and traits such as light eye and hair color, freckling and nevus density when assessing overall melanoma risk, but did not consider risk for specific melanoma subtypes. There is increasing evidence that two major types of melanomas can be distinguished on sun-exposed skin. One shows macro- and microscopic signs of long-term UV exposure and is specifically highlighted by the presence of solar elastosis, a distinctive change in elastic fibers of the skin. These melanomas with chronic sun-induced damage (CSD) typically originate on the head, neck, and the dorsal surfaces of the distal extremities of older individuals (>55 years of age). They also have a high mutation burden and often harbor mutations in NF1, NRAS, $BRAF^{non\text{-}V600E}$, or KIT. The other major type (termed 'non-CSD melanomas') typically affects intermittently sun-exposed areas such as the trunk and proximal extremities of younger individuals (<55 years of age), and patients do not show marked solar elastosis. In these cases, tumor cells exhibit a moderate mutation burden and a predominance of $BRAF^{V600E}$ mutations. Both types are associated with distinct precursor lesions, 'non-CSD'

with acquired nevi that already exhibit $BRAF^{V600E}$ mutations and 'CSD' with atypical melanocytic neoplasms and melanoma in situ.

Prevention strategies

The effectiveness of UV-absorbing sunscreens in melanoma prevention represents an area of active investigation and offers significant promise for large populations at risk. Studies demonstrate the benefit of sunscreen in melanoma prevention, with up to 50% reduction in incidences. Determining whether additional UV protection could result from improved sunscreens or their contents [i.e. their ability to reduce the formation of reactive oxygen species (ROS)] is of importance.

Prevention strategies should be implemented with the consideration of personal behavior, which is affected by our awareness, education, and interaction with the environment (degree of exposure to sun or indoor tanning).

Knowing why individuals engage in melanoma risk-associated UV exposure behaviors is key to devising methods to improve primary intervention. Work in this area has found that tanning is motivated by psychological factors and can be associated with addictive behavior. A Comprehensive Indoor Tanning Expectations (CITE) scale found that two positive factors (mood enhancement and social approval) and one negative factor (psychological/physical discomfort) predicted future indoor tanning behavior among young women in the southeastern United States. Additional work is necessary to develop working models to understand motivations for melanoma risk-related behaviors across populations. This work then needs to be translated into messages and interventions that address the motivators. It hardly needs to be stated, but banning the use of tanning salons by minors is a straightforward cost-effective mechanism for reducing exposure, and should be a priority for every advocacy organization.

Biological addiction in melanoma risk and prevention

Data from human epidemiologic studies demonstrated the presence of true addictive behaviors following UV irradiation. These studies suggest that frequent use of tanning beds may be associated with "self-treatment" of depressive symptoms and also may satisfy psychiatric DSM (Diagnostic and Statistical Manual for mental disorders) criteria for addictive human behaviors. Animal models have demonstrated induction of beta-endorphin by sun exposure. Collectively, sun-seeking behaviors may represent an evolutionarily selected, hardwired pathway; if so, novel approaches are needed to overcome them.

Empowering behavioral change

Empowering behavioral change is essential to translate prevention knowledge into meaningful action for populations at risk for melanoma. Compliance with melanoma prevention recommendations improves when individuals from hereditary melanoma families are provided with personal genetic test results. Individuals with a personal history of melanoma are most compliant with prevention recommendations. In addition, informing individuals without a personal history of disease that they are carriers of a CDKN2A/p16 mutation leads to improvement of photoprotection, self-skin examination and professional

examination behaviors, in the absence of melanoma diagnosis. Provision of negative genetic test results to non-carriers also improved compliance with some but not all medical recommendations.

Behavior / risk assessment recommendation—By understanding cognitive processes underlying sun exposure behaviors, we may be able to improve communication of risk and empower individuals to comply with prevention recommendations (Table 1).

Approaches for melanoma prevention

Increased understanding of pigment cell biology and molecular mechanisms has enhanced the potential of employing a preventive approach. This approach targets individuals at risk of the disease and uses safe drugs or natural products that may prevent or reverse melanoma development. Specific features of melanoma biology, pathogenesis, and epidemiology make it an ideal model for chemoprevention approaches, including: identification of key targetable signaling pathways, the availability of surrogate disease markers (e.g. dysplastic nevi), the accessibility of skin to perform serial non- to minimally-invasive assessments, and identification of individuals at risk of developing cutaneous melanoma. Challenges, however, remain to be addressed, including: (i) the need to identify drugs with a well-characterized mechanism of action to prevent melanoma, (ii) analyses of drugs already evaluated in humans that rely on validated biomarkers of response as part of future intervention studies, and (iii) identification of targeted risk cohorts based on understanding of drug mechanism and calculating the risk/benefit ratio of the intervention.

Oxidants/pro-oxidants, vitamin D and eumelanin are among examples of chemicals / natural products that have been assessed for their possible effect on melanoma prevention. Those include: (i) NSAIDS (non-steroidal anti-inflammatory drugs): Multiple epidemiological studies have evaluated the role of NSAIDs in melanoma prevention with controversial results. Further studies are thus required to clarify short and long-term effect of NSAIDs and their metabolites on melanocytes and melanoma development. (ii) Statins: Meta-analyses and intervention clinical trials (using clinical and histological endpoints in benign nevi) do not currently support the use of lipid-lowering agents in melanoma chemoprevention. (iii) Sulforaphane: Experimental studies indicate that sulforaphane upregulates antioxidant genes and may affect immune pathways. Further assessment of its possible use is currently underway. (iv) Vitamin D: Several studies point to a possible role of vitamin D supplementation as a preventative agent in vitamin D-deficient patients. However, the complex relationship between vitamin D and melanoma risk/outcome (higher UV exposure results in higher serum vitamin D levels but also higher risk of skin cancer) is recognized and need to be considered in these evaluations. A 7-year follow-up trial evaluating the effects of calcium and vitamin D supplementation did not reveal a difference in incidence of non-melanoma skin cancer or melanoma rates (except in a sub-cohort of patients with a history of non-melanoma skin cancer). Further studies that take into consideration sun exposure and standardization of molecular markers of response are needed. (v) Antioxidants: The effect of systemic antioxidants as melanoma chemoprevention drugs remains controversial. A growing body of data suggests that antioxidants, including selenium, may promote rather than prevent cancer, an outcome supported by data from large, randomized

controlled trials testing selenium and vitamin E in non-melanoma cancers. Interestingly, both mouse models of melanoma and xenografts of human melanoma in mice show that relief from oxidative stress by treatment with the antioxidant N-acetyl cysteine leads to disease progression, suggesting that these approaches be reassessed in carefully crafted human and animal-model based studies.

Overall the current chemoprevention data suggests that (i) there is no clear evidence to support any particular agent for widespread use in melanoma prevention solution; (ii) in the case of antioxidants recent evidence suggests, promotion, rather than prevention of melanoma metastasis in certain experimental settings

Emerging opportunities / considerations

Pigmentation modifiers—The use of small molecules to induce the synthesis of eumelanin in skin as a means of protecting against skin damage has been proposed and carried out via topical administration of the drug forskolin to mice genetically engineered to be red-haired and light-skinned. This strategy seeks to mimic inherent protection against cutaneous melanoma incidence seen in humans with dark skin pigmentation. The approach was found to offer mutant mice significant protection against UV-induced mutagenesis and skin carcinogenesis, although it was tested in a squamous cell carcinoma model. Human trials have been performed using alpha melanocyte stimulating hormone and active peptides derived from MSH that similarly lead to darkening the skin. These agents may have substantial off-target effects, including promotion of growth of nevi, which will need to be considered in the design of subsequent trials. Approaches to identify safe agents capable of modulating eumelanin synthesis in human skin could provide tools to prevent both melanoma and non-melanoma skin cancers and serve as a more general cutaneous photoprotection method in various contexts (Table 1).

Microbiome considerations—A patient's microbiome may also play a key role in melanoma development and response to therapy. Currently, researchers are asking whether a specific subspecies of gut bacteria is associated with resistance to melanoma development and whether the presence of select bacterial species correlates with improved therapeutic outcomes. Though these initial studies demonstrating the impact of the microbiome on cancer therapy (including melanoma) are encouraging, they need to be validated and extended to higher resolution (for example, understanding the mechanisms linking the gut microbiome with immune responses). Notably, while the gap between mouse and human microbiota is recognized, substantial efforts are needed before one may project the mouse-based studies to human settings. The complexity lies not only in the number of bacterial strains, but equally important, in the relationship among them (one bacterial community affecting another). Further studies are required to map different bacterial communities in the gut and assess their effect on the immune response and the tumor microenvironment. Altering the bacterial landscape in a manner that would antagonize tumor development or favor therapy, possibly via use of probiotics, is a challenge that would deserves proper recognition and attention by the scientific and medical communities at large (Table 1).

Chemoprevention Recommendations: There is a clear need to perform additional studies that incorporate genetic and epigenetic data, dietary, behavior, and sun exposure data collection in their design (Table 1). Adequately powered prospective, randomized trials are required to assess the implication of regular use of such chemicals. Prior to initiating clinical studies, it will be critical to establish the effective dose and timing of the drug, the optimal delivery method, which biomarkers are best surrogates of efficacy, and which population of patients should be included or excluded. Critical considerations of these studies should be the impact of the tested chemical on skin cancer (basal and squamous cell carcinomas) versus melanoma, and potentially harmful off-target effects. Such studies will require large, risk-selected cohorts and proper stratification across the various arms of prevention studies to determine efficacy. It is expected that such an investment could reduce the overall burden of the disease and minimize the number of individuals in need of treatment.

Detection/ Early Diagnosis

Melanoma consists of several disease subtypes that differ in their epidemiology, clinical manifestation, pathogenesis and clinical course. On sun-exposed skin at least two different pathways are distinguished, and other subtypes with distinct features arise from the choroidal tract of the eye and meningea, as well as from glabrous (non-hair-bearing skin) and mucosa. Additional work is required to precisely delineate these subtypes, define their individual predispostion to environmental factors (such as UV exposure), and their respective molecular evolution from precursor lesions. A deeper understanding of the different pathways for melanoma formation and clearer definitions of melanoma subtypes could improve risk prediction and prognostication.

As melanoma screenings efforts continue to expand, it is critical to improve diagnostic accuracy of both clinical and histopathological criteria to minimize the risk of harm related to screening methods. Histopathological diagnosis remains the gold standard but has proven limitations, highlighting the need for identification of additional markers that can assist in diagnosis. Several studies show sizeable disagreement among pathologists regarding the diagnosis of melanoma and benign melanocytic nevi, with one study reporting up to 15% discordance. Thus, it is imperative to improve diagnostic accuracy to decrease false positives that might result in unnecessary surgery, adjuvant therapy, and psychological harm. It is even more critical to reduce the proportion of false negative diagnoses that could increase morbidity and overall survival. Current work that addresses discrimination of melanoma from benign or low-grade dyplastic nevi is based on gene expression or DNA copy number changes by comprehensive genomic hybridization (CGH) or fluorescence in situ hybridization (FISH), while gene expression profiling (GEP) based analyses is gaining traction.

It is expected that established melanoma risk phenotypes and genotypes will differ among melanoma subtypes. For example, high mole density is positively associated with non-CSD melanoma, whereas actinic keratosis and solar lentigines are positively associated with CSD melanoma. The same holds for genetic variants, which are likely to reveal similar differences between the subtypes. While the precise definitions of these subtypes are still emerging, sufficient phenotype and genotype stratification markers are now available to allow studies

to assess associated risk. Such studies could help refine criteria to identify individuals at high risk for either CSD or non-CSD subtypes and to improve disease education for patients and healthcare providers.

A similar rationale applies to early recognition of tumors or high-risk precursor lesions and staging criteria for established melanomas. The current ABCDE (A- asymmetry; B- border irregularity; C- color variation; D- diameter > 6mm; E – evolving lesions) diagnostic criteria could be improved by tailoring them to different subtypes and risk groups. Moreover, AJCC (American Joint Committee on Cancer) staging criteria, which are also currently in use, may provide improved prognostic information once different criteria or cutoffs for different subtypes are developed.

Diagnosis recommendation

(i) While some CGH/FISH/GEP are already in use clinically or are being validated, further studies are necessary to develop more accurate, cost-effective, and practical methods to improve the accuracy of melanoma diagnosis.

(ii) Development of refined risk phenotypes could be improved by increasing the sensitivity and specificity of markers tailored to melanoma subtypes (iii) Additional standards useful to identify individuals with increased risk could include clinical or molecular markers indicating mutation load in skin as well as biomarkers for immune-competence and the state of the tumor stroma. (iv) Improved understanding of how melanomas evolve from precursor lesions will allow development of objective criteria for diagnosis based on the number and type of pathogenic mutations or perturbations in critical signaling pathways. Developing these objective standards will improve diagnosis of primary melanomas and enable classification of intermediate lesions, which cannot yet be accomplished using current methods (Table 1).

Melanoma screening efforts

The vast majority of primary melanomas emerge in skin where they can be readily detected without specialized instrumentation. Screening the general population for skin cancer has been controversial, as it is not yet clear whether this effort will lead to reduced deaths, particularly given the low mortality associated with the most common skin cancers (such as basal cell and squamous cell carcinomas). Thus, programs and policies regarding screening have focused on melanoma—the most deadly form of skin cancer.

A variety of screening programs have been proposed and carried out in the US and abroad. Critical for the success of these programs is the proper public education and the ability of general practitioners to refer patients directly to dermatologists for basic risk assessment. Lack of common protocols hampers the ability to compare screening efforts either between or within countries.

In 2009, the third US Preventive Services Task Force (USPSTF) evaluated worldwide evidence (through 2005) relevant to skin cancer screening by primary care physicians. They rated this screening as “Insufficient” to assess benefit or harm in early detection of melanoma and other skin cancers in the adult general population. No formal randomized and

controlled melanoma screening trials have been conducted worldwide (due to high cost and lack of feasibility). The USPSTF recently conducted a systematic review of worldwide evidence from January 1995 through June 2015, again assigning an “Insufficient” grade to melanoma screening by primary care physicians in the US in the Draft Recommendation. Nevertheless, the USPSTF continues to note the value of screening individuals at highest risk of fatal melanoma and recommends screening of these individuals, along with counseling of parents with young children, as well as young individuals aged 10–24 regarding sun protection and effects of UV exposure on photoaging and skin cancer.

Slip-Slop-Slap (Slip on a shirt; Slop on the 30+ sunscreen; Slap on a hat) was an internationally recognized sun protection campaign in the 1980 in Australia. Later, this initiative was also noted in New Zealand, Canada and the UK. The education of the Australian population is a paradigm that can be followed, given the recognition, appreciation and measures undertaken for sun protection today. “Get Naked” is an example of a campaign spearheaded by the Melanoma Research Foundation over the past couple of years, which was largely conducted through social media or limited advertisements in public places. The simple public health recommendation that one should subject oneself to periodical self-examination is expected to increase awareness and early detection of moles or lesions that can be evaluated by professionals soon after. The campaign has resulted in impressive social media attention, although it is too early to assess its impact and effectiveness. At present, there are several ongoing efforts nationwide designed to collect data on the impact of screening on melanoma detection, cost and survival.

Screening efforts recommendations—(i) large-scale, stand-alone media campaigns to encourage high-risk groups to undergo screening and support of state-based demonstration projects that combine media, provider reimbursement, and public education. (ii) Programs should emphasize collaboration with primary care clinicians to improve skin cancer triage and reduce morbidity and cost for all types of skin cancer. (iii) Studies to assess benefits of targeting those at highest risk of fatal melanoma, such as white men >50 years of age, should be conducted (Table 1).

Under reporting

Studies conducted in 2008 and 2009 raised concerns about melanoma under-reporting, with rates estimated in the range of 30–40%, while acknowledging that the overall magnitude of the problem remains unknown. A more recent study in the state of Arizona indicates that under-reporting rates might be as high as 70%. In the US, management of cancer data generally falls under the responsibility of state cancer registries, agencies that rely solely on providers submitting appropriate forms to them. Cancer incidence rates are calculated from data maintained by state cancer registries, and the accuracy of this information is highly dependent on the actual reporting of cancer cases from community sources, including physicians. The potential for under-reporting is especially high for melanoma, since it is frequently diagnosed and treated in outpatient settings and pathology may be read out of state.

Single lesion assessment

Most single lesion evaluation is carried out through unaided skin examination and dermoscopic assessment. New technologies relevant to non-invasive melanoma diagnosis are emerging with the goal of increasing sensitivity and specificity of current practices. Among technologies that attempt to enhance and/or automate current practices are in vivo confocal microscopy, multispectral imaging, and electrical impedance. Challenges related to these approaches include the need for further validation to ensure diagnostic accuracy of these modalities, the demands of learning a new technology, variability among readers, lack of comparative trials between new technologies, and cost. In addition, dermatology practices seek to increase the efficiency of patient flow, and introduction of emerging technologies may slow this. Thus for successful adoption of new technologies it is necessary to identify barriers in implementation and implement systems that offer a clear advantage to current diagnostic approaches. In addition, many of these new technologies are unlikely to be widely available in the primary care setting, suggesting that they may enhance sensitivity and specificity of melanoma diagnosis on per-need basis.

Regional and total body imaging

Considering the rapidly emerging improvement and accessibility to digital imaging technologies, there is a need to effectively standardize the use of digital imaging in dermatology and other specialties when capturing regional and total body photographs. While several medical specialties have specific DICOM (Digital Imaging and Communication in Medicine) standards for digital communication, this is not the case for dermatology. An initiative established by the International Society for Digital Imaging of the Skin (ISDIS) seeks to standardize current practices for image capture, terminology, storage, and privacy issues surrounding digital imaging of patient skin (“International Skin Imaging Collaboration (ISIC): Melanoma Project”). The value of photographic digital imaging has been more consistently evaluated in settings where patients at high-risk for melanoma have undergone regional/total body imaging or when skin lesions have been monitored short term. Developing standardized parameters is critical as new systems capable of automated and semi-automated total body image capture are emerging.

Consumer-based early detection through mobile technologies

Mobile phones have revolutionized communication around the world, not only through voice-based communication but also through the development of phone-based social media (such as Twitter and Instagram) and development of healthcare-related mobile applications (apps). Phone-associated technologies, particularly the camera and the global positioning systems (GPS), enhance specific performance capabilities of apps. The app industry is rapidly entering the healthcare space, and because skin is so accessible, skin lesion photographs are commonly sent to physicians, who are being asked to evaluate these photos clinically. At this time, little data is available regarding the validity of such an approach. There are now over 100 melanoma detection apps available in app stores around the world, but none have yet been shown to demonstrate the capacity to diagnose melanoma.

Need for increased specificity and healthcare cost implications

A critical consideration when assessing current melanoma screening practices relates to the number of procedures performed to diagnose the 76,100 cases of melanoma reported in the U.S. in 2015. Current estimates indicate that approximately twenty-five biopsies are performed for every diagnosis of melanoma rendered. By extension, this implies an estimate of 2,283,000 biopsies performed per year as part of current melanoma screening practices. However, under-reporting of melanoma is estimated to range from 40 to 70%. Assuming an average of 55% under-reporting rate across all states and a sustained biopsy rate of 25 procedures for every melanoma diagnosed, an estimated 4,073,333 biopsies may be performed annually in the US to diagnose 169,111 melanomas.

An area of significant opportunity is detection of “amelanotic” melanoma. This tumor subclass was recently found associated with higher mortality than darkly-pigmented melanomas, probably due to diagnosis at a later (thicker) stage. Recent animal model-based studies suggest that in some amelanotic melanomas, dark pigment is replaced with pheomelanin. Imaging of pheomelanin may allow one to identify these more dangerous lesions.

Diagnosis technologies / reporting recommendations—(i) Modification of the reporting along with effective education of physicians for the need to report melanoma cases should increase the number of reported cases. (ii) Effectively standardize the use of digital imaging in dermatology and other specialties when capturing regional and total body photographs. (iii) Increase our ability to diagnose aggressive melanoma subtypes and to minimize morbidity associated with the comparatively larger number of unnecessary skin biopsies (Table 1).

Dormancy and Early Metastasis

It is well accepted that melanoma cells can be shed early from a primary tumor and remain silent or "dormant" as micrometastatic foci for periods ranging from under a year to decades. Clinically, dormancy describes the status of microscopic metastases prior to progression to overt cancer. Tumor dormancy is thought to depend on at least three elements: (1) cellular dormancy, in which tumor cells survive in a quiescent, slowly dividing state; (2) angiogenic dormancy, in which lack of vascularization holds growth of micrometastases in check and promotes programmed cell death, known as apoptosis; and/or (3) immune-mediated dormancy, where the immune system continues to limit the tumor population. Disruption of these processes can awaken dormant micrometastases and stimulate their expansion into overt metastases, leading to patient morbidity and mortality.

Maintenance of a dormant state likely requires intrinsic or "cell autonomous" factors and extrinsic microenvironmental cues. The latter can be derived from the vascular and lymphatic systems, the presence of inflammatory cells, or the activity of stromal and support cells. Relevant to the immune system, "immunoediting" may occur, a process in which most immunogenic tumor cells are eliminated, leaving a poorly immunogenic, dormant population. In cancer types other than melanoma, chemotherapies (a topic covered in another section of this report) have been shown to modulate either induction or escape from

dormancy. The adaptive immune system may also regulate tumor dormancy. Here, we view dormancy as an organ-based process and will discuss issues related to dormancy that must be considered when designing interventions.

Factors regulating dormancy

It is likely that complex mechanisms of crosstalk between cancer cells and their microenvironment and vice versa, initiate and establish tumor cell dormancy. In turn, mechanisms promoting cell survival and evasion of the immune system may be enhanced and potentially altered as a response to therapeutic agents. As a framework for future studies, the following stages of dormancy and mechanisms underlying them have been proposed: (i) Establishment of competency for a dormant state. Shed melanoma cells may be able to home directly to favorable metastatic sites, and many of those regions may favor tumor cell survival by creation of a pre-metastatic niche. However, like other tumor cells, melanoma cells may exploit reservoirs such as bone marrow as an intermediate site on the journey to a target organ. The possibility that dormancy can be also induced following exposure to a particular therapy cannot be excluded. (ii) Mechanisms governing long-term survival of tumor cells at metastatic sites. Cell survival mechanisms may be switched on either in solitary quiescent cells or in a small number or colony of cells. Such mechanisms may foster resistance to cytotoxic chemotherapy. (iii) Self-renewal mechanisms that maintain the capacity for tumorigenesis. These activities might allow a balance between cell proliferation and cell death. Both intrinsic and extrinsic (from the stroma, the vasculature, and/or the immune system) signals likely govern this balance. Activation/suppression mechanisms that affect aggressive outgrowth. A combination of intrinsic and extrinsic factors, including microenvironment, angiogenesis and immune-surveillance are expected to impact the nature of outgrowth.

Noteworthy issues relevant to melanoma dormancy

Our current understanding allows us to define similarities/differences between dormancy in melanoma and other tumor types. Growing evidence supports the influences of melanoma cell plasticity and stem-like properties on dormancy, yet, precise factors that underlie the switch to dormant cells are not known. Likewise, the relationship between melanoma dormancy and physiological stem cell dormancy is an important aspect that requires further study.

In recognizing the nature and significance of melanoma dormancy, it is conceivable that "re-awakening" dormant cells could make them susceptible to immunological and/or targeted drug therapy. In this context, the role of the premetastatic niche in establishing or awakening dormancy is an important area to explore. Lastly, one cannot ignore the importance of the bone marrow as a nurturing environment for the dormant melanoma cells. At present, the molecular analysis of melanoma dormancy lags significantly behind that of breast and prostate cancers. Research directed at filling this gap is required.

Clinical considerations in assessing melanoma dormancy

With high cure rate in patients subjected to surgical therapy, one may question the significance of dormancy in such cases. Notably, we do not know whether patients that were

cured lacked dormant melanoma cells. Thus, with our current understanding it will be important to assess dormancy during all three phases of clinical investigation: (i) detection/diagnosis, (ii) prediction/prognosis, and (iii) treatment. A better understanding of tumor dormancy at these points in time would allow us to block awakening mechanisms. It is anticipated that tumor dormancy will be most efficiently targeted in patients with earlier stage disease, provided that effective treatment regimens are available. Thus, an analysis of whether current regimens are effective against dormant tumor cells is warranted. New approaches to adjuvant therapy, either pre or post surgical removal of the primary tumor, also need to be considered. Finally, there is a critical need to identify blood-based biomarkers and novel imaging strategies that may indicate the status of a patient's dormant tumor cells, as well as novel imaging strategies to detect them.

Development and exploitation of models of melanoma dormancy

It is evident that animal models can significantly complement analysis of clinical samples by providing a platform to define basic mechanisms underpinning tumor initiation, as well as to serve for pharmacological screens. However, effective models of tumor dormancy are rare and must be established for physiologically-relevant studies. Based on the already well-appreciated heterogeneous and plastic nature of melanoma, dormant cells in this disease will likely have inherent properties that require tailored genetic engineering.

The mouse is the most well-characterized system available. Cell lines that exhibit dormant behavior when engrafted into mice have been described, and one mouse melanoma dormancy model has been established in the context of constitutive RET activation. However, zebrafish models may offer a complementary alternative. In either case, care must be applied to develop models most representative of conditions underlying dormancy of human tumor cells. More challenging is the development of cellular models (namely, genetically-matched cell lines with a distinct potential for dormancy) that recapitulate at least some aspects of the physiology of human melanoma. Such systems, which have been described in breast cancer, would represent a tremendous advantage in understanding mechanisms associated with awakening of dormant melanoma cells.

Characteristics and needs of tumor dormancy models include—(i) Tumor cell dissemination to organs that are the most frequent targets of human melanoma metastasis; tumor-microenvironmental interaction; (ii) Methodology capable of identifying proliferative versus silent cells or cell clusters in vivo; (iii) Immunocompetence to assess immune contributions (e.g. inflammatory cells) and the possibility to evaluate antigen-specific responses; (iv) Capability to evaluate genotype-specific effects on dormancy; (v) Ability to evaluate the microenvironment of micrometastases, including ECM, target organ cells, endothelial cells, pericytes, inflammatory cells, and cancer-associated fibroblasts; (vi) Ability to study effects of aging on dormancy; (vii) Heterogeneity of micrometastases and their primary melanoma of origin; (viii) Ability to employ an on/off switch from dormant micro- to macro-metastases; (ix) Ability for live imaging by non-invasive methods or by intravital microscopy; (x) Capability to conduct whole-body imaging of angiogenesis and lymphangiogenesis (e.g. by exploiting VEGFR3-driven luciferase knock-in models); (xi) Methodology to image metastatic and premetastatic niches; (xii) Ability to test how

mutational burden affects dormancy; (xiii) Ability to detect conversion from dormant to growing cells in live animals.

Dormancy model tools and approaches currently available and adaptable include—*(i)* GEM models. Use of these models could be coupled with surgical removal of the primary melanoma. Incorporation of Cre-based fluorescent reporters would add value to this model. (ii) Grafted models. These include orthotopic subcutaneous implants for cutaneous melanoma models, with and without surgery. Other implantation strategies can include left ventricle or tail vein injection. For uveal melanoma, injections into the eye uveal tract are feasible and may be pursued as an anatomically-relevant setting. Although, it would certainly be more advantageous to employ an immunocompetent model system, human melanoma cells and tissue can be grafted into immunocompromised host mice. Future availability of host mice with humanized immune systems will greatly enhance the value of this approach. Availability of appropriate cellular models that mimic genetics of the human disease would also add value to this general approach. (iii) Genetic engineering. This will include CRISPR-based gene editing as well as transposon-based mutagenesis. (iv) Multidimensional “omics” analyses. These technologies can be focused on isolated single cells and include analysis of RNA, DNA, epigenetic changes and metabolism. (v) Imaging modalities. Multiple modalities are currently available, including bioluminescent imaging, fluorescent stereomicroscopy, 2-photon microscopy, light sheet microscopy, micron-sized nanoparticle-based imaging, and quantitative histological imaging. (vi) Reporter tools. Numerous reporters are available that can distinguish between the vasculature, macrophages, fibroblasts, lymphocytes, and other cells or tissues. Importantly, more complex reporter systems are already available that can separate proliferating from quiescent/dormant cells in vivo. (vii) Monitoring. Development and incorporation of better tools for assessing dormancy in clinical trial design, such as measuring and profiling CTCs, circulating tumor DNA and exosomes, assessing bone marrow for dormant cells are important. The ability to simultaneously identify and isolate dormant and proliferating populations from several metastatic sites is also of relevance for both cutaneous and uveal melanoma, and development of improved tools is a priority.

Targeting dormancy

Targeting dormant cells poses significant challenges, as one needs to consider the partial elimination of some while awakening others. Their select targeting is of equal challenge given their distinct state of proliferation and metabolism. Here, immunotherapy could be useful if dormant cells express antigens recognized by the immune system; however, a dedifferentiated state may mask dormant cells. Dormant cells may upregulate several cell survival pathways that can also oppose drug response. Moreover, the wiring of pro-tumorigenic pathways may be distinct depending on the specific environment (“conditioning”) of the pre-metastatic niche. Therefore, a better understanding is needed on how available chemo- or immuno-therapies impact either establishment or awakening of dormant cells. The following are possible strategic approaches: (i) Prevention. The goal of this approach is to keep cells in an indefinite dormant (G0) state. In this context, it is of relevance to note patient-related compliance issues, which drops if treatments extend beyond 6 months. Therapy would need to be safe and tolerated over years of administration.

Differentiation therapy may also be considered in an effort to induce a permanent G0 state for dormant cells. (ii) Awaken and target dormant cells. This approach requires identifying pathways underlying awakening to push quiescent cells out of dormancy. Those cells would then be targeted and killed using conventional anti-proliferation therapy. This approach is risky as it could result in generation of highly aggressive cells, hence complicating clinical tests due to ethical considerations. (iii) Eradicate all dormant cells. This approach would require identification of single or combination-based therapies with a broad spectrum of action. Some approaches to be considered include: (iv) Target survival pathways that sustain dormant cells; (v) Target embryonic pathways that maintain the dormant state (vii) Target the "dormancy niche" by altering cell adhesion and/or cell to cell communication; (viii) Trigger immunogenic protein expression in dormant cells, possibly by inducing presentation of differentiation antigens; (ix) Eradicate dormant cells using monoclonal antibodies specific/selective for tumor antigens coupled to toxins, a-particle emitters or other toxic substances; (x) Implement adjuvant therapies to attack dormant cells early, perhaps at primary tumor resection; (xi) Extend the length of treatment, depending on drug toxicity, which may sustain dormancy, quiescence and or differentiation.

How to best apply translational research to assess tumor dormancy in patients?

Tumor dormancy can be studied in retrospective and prospective cohorts of patients. These can include patients with thin melanomas and positive sentinel nodes and poor clinical outcome, versus those with similar histopathological manifestations but a positive prognosis. Cohorts from randomized clinical trials are of highest value. Such specimens are already available though highly dedicated clinical teams and are needed to identify and annotate cohorts of interest. Importantly, this effort will require sharing of samples/datasets (ideally through controlled repositories) to foster collaboration among multiple investigators and sites to increase sample size and statistical power. As tumor material may be limited, it will be important to prioritize samples (primary lesions, metastases, blood) and time-points to be analyzed. Similarly, efforts should be dedicated to "downstream analyses", including molecular and immune studies of tumor and blood samples. We also need to define additional potential contributors (e.g. germline signatures of susceptibility/influence of the gut microbiome) to direct experimentation and mathematical modeling. These questions should be addressed by collaborative approaches and coordination with multiple stakeholders, including, policy makers and funding agencies. Specific funding calls will be needed to ensure productive and long-lasting interactions. As we move forward, it will be important to perform these studies via a "co-clinical trials" approach—with parallel studies in man and mouse for trans-species cross-validation of mechanisms and insights gained.

Dormancy Recommendations—(i) Assess early metastasis and tumor dormancy in cohorts of patients with melanoma to better understand activities leading to disease progression. (ii) Develop biologically relevant models of metastatic dormancy in which to conduct mechanistic and functional analyses. (iii) Integrate Data from preclinical studies to inform clinical approaches. (iv) Determine what constitutes competency for a dormant state and what governs long-term survival of dormant cells at metastatic sites. (v) Identify mechanisms that maintain dormant cell capacity for tumorigenesis (vi) Define activation/

suppression mechanisms that influence aggressive outgrowth of dormant cells. (vii) Determine whether dormant cells should be awakened or maintained dormant (Table 1).

Therapy: Status, Challenges, and Opportunities

Advances over the past decade have identified genetic changes that allow stratification of melanomas into distinct groups. Among those, tumors harboring *BRAF* or *NRAS* mutations are most prevalent. Other groups include melanomas with genetic changes in the *NF1, KIT* or *RAC1* genes. The genomic landscape of melanoma is also defined by epigenetic changes in complexes of proteins that interact with DNA to regulate gene expression. Some of the latter parallel genetic alterations, while others reflect a cellular response to environmental stimuli that drive cells to adapt to harsh conditions (such as lack of nutrients or chemotherapeutic drugs). While the analysis of somatic mutations has generally focused on their effects on protein functions, there is growing interest in their potential immunological effects (e.g. neoantigens are potent immunogens).

In parallel to an improved understanding of the genetic basis of this disease, the treatment of patients with metastatic melanoma has undergone a paradigm shift in the last 5 years. Prior to 2011, only two therapies (dacarbazine and high-dose bolus interleukin-2 [IL2]) were approved in the US to treat these individuals. Both achieved clinical responses in <15% of patients, but neither demonstrated significant impact on patient survival in a randomized trial. Thus, until very recently the only real option for patients with metastatic melanoma was to participate in a clinical trial of an experimental drug or treatment. However, after a prolonged period of failed trials, the US FDA granted regulatory approval to 10 new therapeutic regimens for patients with metastatic melanoma between 2011 and 2015, events that were both unprecedented and exciting. Melanoma patients and their physicians now have a plethora of therapeutic options at their disposal.

Despite major progress, the need for high-quality clinical and translational research remains. Little is known about how best to match patients to therapies with the greatest probability of promoting long-term disease control, and overcoming resistance to existing therapies remains a pressing need. Thus, there is now a critical opportunity to build on the growing foundation of knowledge to translate predictive biomarkers into diagnostic tests, to develop tools to discern mechanisms of resistance, and to rapidly develop next generation therapies.

Targeted therapies

The development of approved targeted therapies has been driven by significant advances in understanding the diverse molecular mechanisms of melanomagenesis. In particular, availability of therapies for patients with $BRAF^{V600}$ mutations, which occur in ~45% of non-acral cutaneous melanomas, has been promising but also identified key challenges that must be overcome to maximize long-term clinical benefits of this strategy. Combined treatment with BRAF and MEK inhibitors as a therapeutic approach achieves RECIST (response evaluation criteria in solid tumors) responses in ~70% of patients with $BRAF^{V600}$ mutations and disease control in virtually all patients. However, most treated patients will eventually exhibit disease progression due to a constellation of resistance mechanisms emerging from tumor heterogeneity within an individual patient. To date, no targeted

therapies have demonstrated significant clinical efficacy in patients whose disease progresses following BRAF/MEK inhibition, thus driving an active area of research.

In addition to new mutations, epigenetic factors and tumor interaction with the microenvironment likely play roles in drug resistance, activities that present diagnostic challenges but also new therapeutic avenues. Diagnosis in particular is complicated by the heterogeneity of resistance. Thus, while much can be learned from biopsies, more global diagnostic tools (such as markers detectable in blood or molecular imaging) are needed to stratify “types” of resistant patients in order to develop rational, effective approaches. Patient outcomes may also be improved by interrogation of targeted therapy dosing strategies, including intermittent approaches, which delay resistance, or by higher dosing in terms of combination therapies. Higher dosing may be particularly relevant to central nervous system (CNS) metastases, which remain a significant therapeutic challenge. There is also an unmet need to identify markers to identify patients who will achieve a more durable benefit from BRAF and BRAF/MEK inhibition, a phenomenon known to occur in 10–20% of BRAFi-treated patients and up to 30% of BRAF/MEK-inhibitor-treated patients.

Finally, it is also critical to identify effective strategies to treat metastatic melanoma in patients lacking *BRAF*^{V600} mutations. In depth studies of cutaneous melanomas have identified several additional potentially targetable genes and pathways. The lessons learned from the still-evolving treatment of patients with BRAF^{V600} mutations should facilitate progress in developing therapies aimed at patients who lack them, most of whose melanomas harbor activating *NRAS* or inactivating *NF1* mutations. Both alterations perturb RAS signaling; thus a key question, which is also relevant to multiple other cancers, is whether to directly target RAS or consider targeting of effectors of RAS signaling, such as RAF protein kinases or phosphatidylinositide (PI)-3’ kinases. Initial molecular profiling studies also show that non-cutaneous melanoma subtypes have distinct biologic properties. This is particularly true of uveal melanoma, which is characterized by one of the lowest mutation rates of all solid tumors and by a distinct set of somatic alterations. There are currently no effective therapies available to treat this condition, presenting both a need and an opportunity.

Immunotherapy

Immuno therapy posits that one does not need to treat tumor cells but rather prime a patient’s immune system to more efficiently attack the patient’s tumor. This approach has revolutionized melanoma therapy and resulted in unprecedented rates of long-term disease control and survival in patients with metastatic disease. However, multiple challenges and opportunities remain to optimize this therapeutic approach.

The clinical experience with high doses of the cytokine IL2 provided the proof-of-concept that immunotherapy can result in long-term disease control and survival in metastatic melanoma patients, albeit only in a very small percentage of patients and with very high toxicity in all treated patients. However, the clinical development of immune checkpoint inhibitor therapy has made such outcomes a reality for an increasing number of patients. For example, long-term follow-up with ipilimumab (Ipi), which targets CTLA4, indicate that ~20% of patients survive at least 3 years after initial treatment, with current data suggesting

that few patients relapse and die after that benchmark. This benefit is balanced by the fact that Ipi treatment has a low clinical response rate (~10%), a slow onset of action, and a significant rate (up to 25%) of autoimmune toxicity. The approved single-agent anti-PD1 antibodies nivolumab (Nivo) and pembrolizumab (Pembro) achieve clinical responses in 30 to 45% of patients, including individuals who have failed Ipi either due to disease progression or drug toxicity. Nivo and Pembro are also associated with much lower rates (<10%) of autoimmune toxicity than Ipi. Long-term survival data is still pending for these agents, but many clinical responses to PD1 antibodies appear to last for at least the duration of active treatment thus far (2 years). Randomized trials with Nivo and Pembro demonstrated significant improvements in safety, response rates, and in overall survival compared to Ipi. It remains to be determined which patient subpopulations will derive long-term benefit from each therapy.

Questions remain about how to further improve the efficacy of these agents. Current evaluation of combined Ipi + Nivo treatment suggests significantly increased response rates, with 50 to 60% of patients responding positively. However, the regimen is also characterized by a high rate of autoimmune toxicity. Clinical trials are under way to test other combinatorial approaches, with success defined not only as improved efficacy but safety and tolerability. Complementary efforts are aimed at understanding resistance to immunotherapy. Initial findings suggest that PD1-resistant melanomas are characterized by markedly lower T-cell infiltration and by lower tumor inflammation, revealing a potential early pharmacodynamic endpoint useful to assess in clinical trials with new therapies and combinations. Molecular studies also show that melanomas with a relatively low mutation burden are less likely to respond to Ipi, although this finding has not yet prevented clinicians from treating patients with this therapy. Molecular analyses identified other oncogenic and targetable pathways in tumor cells that may promote resistance to immune recognition, infiltration, and tumor killing, and trials combining MAPK inhibitors with immunotherapies are under way. Finally, there are many other key regulatory molecules that have been identified on T cells. These molecules may have roles not only as therapeutic agents, but could potentially also be biomarkers of efficacy, resistance, and/or toxicity.

Opportunities

Clinical therapy for melanoma is ripe with challenges that, if met, could further improve disease outcomes. One low-hanging fruit is the need for clinical interrogation of alternative dosing strategies for currently available agents. For targeted therapies, preclinical studies support the idea that intermittent strategies may slow or prevent drug resistance. For immune therapies, the optimal frequency and duration of therapies is unclear. Testing of alternative dosing strategies could have safety benefits and, in fact, may be necessary if significantly higher-order combination regimens are needed to maximize long-lasting disease remissions. Fiscal benefit could also drive prioritization of treatment strategies in an increasingly cost-confined healthcare system. Assessment of dosing strategies would clearly benefit greatly from new markers that accurately predict clinical benefit early in treatment.

Dramatic progress seen in treating patients with distant metastases suggests that patients with regional disease or even high-risk localized melanoma could experience similar

benefits. In particular, the development of reagents with high response and disease control rates with minimal toxicity presents an opportunity to safely explore neoadjuvant approaches for patients with surgically resectable disease. Neoadjuvant treatment may provide significant clinical benefit not only by reducing the morbidity and/or complexity of surgical procedures, but also by providing information to guide whether a therapy is beneficial and should be continued in the adjuvant setting. A neoadjuvant approach also provides a chance to acquire high-quality biospecimens to analyze resistance mechanisms, which remains challenging in stage IV patients. Neoadjuvant evaluation of early-stage investigational agents could also rapidly evaluate whether that reagent achieved significant target inhibition at clinically-tolerated doses. Finally, the demonstration of long-term clinical benefit from short-term neoadjuvant treatments may also establish a more efficient paradigm to evaluate and potentially approve new therapies.

In contrast to recent therapeutic advances, the development of molecular and/or immune diagnostics to guide clinical care remains largely unrealized. While many research efforts are underway to identify individuals with stage IV disease who are most likely to benefit—or not—from current systemic therapies, there is a strong rationale to also identify patients at greatest risk of side effects. Improved biomarkers will also be critical for the rational use of systemic therapies in patients with earlier stage disease, particularly given the high cost of most new therapies. These studies should be complemented by efforts to improve risk models for earlier stages of disease and to guide appropriate selection of patients in which the risks and costs of aggressive treatment are justifiable.

Heterogeneity within and between tumors presents a significant challenge for overcoming resistance to therapies. While currently available collections of tumor biopsies remain essential to research, the development of non-invasive biomarker strategies would be clinically beneficial. For example, blood-based biomarkers could be a powerful adjunct to current surveillance strategies for patients with early stage disease. For patients receiving systemic therapies, sensitive blood-based response markers could rapidly and rationally guide treatment decisions and expedite evaluation of new strategies. In addition to blood-based markers, new imaging approaches capable of assessing key disease outcomes, such as immune cell infiltration, could also have tremendous clinical impact.

Progress seen in clinical trials and regulatory approvals largely reflects the experience in non-acral cutaneous melanoma patients without significant co-morbidities. There is a need for increased investigation relevant to populations previously excluded or under-represented in landmark trials. For example, clinical trials in patients with significant co-morbidities, including autoimmune disease and CNS involvement, will help guide treatment of real-world patient populations. The distinct molecular biology of non-cutaneous melanoma subtypes, including mucosal and uveal melanoma, also provide a rationale for focused investigations in these populations.

With the growing understanding of melanoma cell biology, the tumor microenvironment, and the role/regulation of the immune system in cancer control, a large number of new and exciting drugs are now at various stages of clinical development for this disease. Yet, with several drugs that improve survival (but cure few) already widely available in clinical

practice, determining and validating surrogate clinical endpoints for long-term efficacy is an urgent need to optimize the design and conduct of clinical trials. Such improvements will ensure that drugs with significant efficacy will be available to patients in a timely manner.

Therapy Recommendations—(i) Develop experimental models to explore novel immunotherapy and signaling based therapy approaches that take into account the genetic and biologic signatures of the disease. (ii) Identify mechanistic basis of intra-tumoral heterogeneity and develop strategies to overcome this clinical obstacle. (iii) Identify and validate biomarkers to select patient sub-groups for targeted therapies. (iv) Identify biomarkers for selection of 2nd line target therapies in for treatment-resistant tumors. (v) Improve efficacy, safety and tolerability of the current generation of checkpoint inhibitors and develop biomarkers for more precise selection of therapies.

The path forward

There remains a critical need to encourage participation in clinical trials in the melanoma patient community. Despite many regulatory approvals over the last 5 years, there remains an unacceptably high rate of treatment failure and death from this disease. Melanoma researchers must partner with patient support and advocacy organizations to communicate this message, and find ways to optimize the ease and safety of participation in clinical trials. This message must also be communicated effectively to funding agencies to ensure continued progress. Progress also critically depends upon collaboration and cooperation with pharmaceutical companies, particularly in designing and supporting innovative trials that may provide new insights.

Ample evidence now supports the idea that there is significant overlap between the regulation of oncogenic signaling and the anti-tumor immune response, and that both determine the efficacy of (or promote resistance to) targeted and immune therapies. In the future, preclinical models must be developed that allow concurrent evaluation of both molecular and immune factors and include dedicated analysis of both in experimental designs. Clinically, there is a need to systematically evaluate both the optimal sequence of and proper combination of targeted and immune therapies to identify safe and effective strategies for patients. It is likely that subsets of patients will benefit differentially from these approaches, and thus there is a critical need for infrastructure to collect and annotate high-quality biospecimens. Furthermore, such studies should incorporate analyses of both tumor and host factors, such as germline polymorphisms and the patients' microbiome.

In addition to our appreciation of drug combinations, we are also in an era that requires multi-disciplinary clinical care and expertise. For example, new opportunities for neoadjuvant therapy will be most impactful if there is close collaboration between medical oncologists, surgical oncologists, and pathologists. There are likewise opportunities for collaborative investigations that include radiation therapy and other interventional modalities; these are just beginning to be realized but will likely expand significantly. Importantly, the growing list of therapeutic options across the melanoma continuum requires multidisciplinary input in patient care and in design of clinical research. Similarly, close

collaboration and communication between clinical and laboratory investigators are essential to expedite progress in the field and provide a strong rationale for new clinical studies.

Relevant to development of future treatment strategies, there is interest in cellular machines that normally maintain cellular homeostasis but are subverted in tumor cells to promote survival. Thus far, these approaches, which are equally relevant to melanoma, focus on five complex biochemical processes: (1) the initiation complex for protein translation; (2) the unfolded protein response (UPR), including the cellular response to misfolded proteins (also part of the ER stress response); (3) the spliceosome, which functions in mRNA splicing and hence gives rise to novel proteins, some of which may underlie cancer; (4) the apoptotic machinery, which is has already been shown to regulate the responsiveness of melanomas to targeted therapy; and (5) the machinery of autophagy, which may regulate the response of melanoma cells to targeted blockade of pro-tumorigenic signal transduction pathways. Ongoing studies should define activities of these complexes in drug resistance or metastasis and begin to identify reagents to target them.

Table 1

The 2016 Road map for Melanoma: Challenges and Opportunities

Prevention	
•	Define challenges and opportunities in context of environmental exposure and individual (epi)genetic makeup
•	Incorporate genetic, epigenetic, dietary, behavior and sun exposure data in design of clinical evaluations
•	Define the impact of UV wavelengths / filters and their optimal uses (sunscreens)
•	Understand cognitive process underlying sun exposure behavior
•	Improve communication with and education of “at risk” individuals
•	Understand and develop means for possible control of melanins / pigmentation
•	Define the microbiome: possible impact on the immune system and melanoma development.
Early detection / Diagnosis	
•	Develop better tools to identify melanoma earlier
•	Develop methods to identify precursor lesions at high risk for progression to melanoma
•	Develop melanoma subtype-specific early detection algorithms (à la ABCD) for patients and providers
•	Develop melanoma subtype-specific staging criteria for improved prognostication, and melanoma subtype-specific risk pheno- and genotypes
•	Establish more accurate cost effective methods for diagnosis
•	Improve reporting and standardize use of imaging technologies
•	Promote media campaigns to educate the public for protection and screening
Dormancy / metastasis	
•	Develop better tools to detect and prevent metastasis
•	Determine what constitutes competency for a dormant state and what governs long-term survival of dormant cells at metastatic sites
•	Identify mechanisms that maintain dormant cell capacity for tumorigenesis
•	Establish genetic models of tumor dormancy to evaluate mechanisms underlying the establishment and reawakening of dormant cells
•	Determine whether dormant cells should be awakened or maintained dormant as part of defined therapy
•	Study dormancy in retrospective and prospective cohorts of patient specimens
•	Monitor dormancy in clinical trial setting, using markers and driver genes identified in experimental genetic models
Therapy / resistance	
•	Identify mechanisms of resistance and therapeutic modalities to overcome it
•	Define mechanisms underlying- and strategies to overcome- intra-tumoral heterogeneity
•	Develop experimental models to explore novel immunotherapy and signaling therapy approaches that take into account the genetic and biologic signatures of the disease
•	Identify biomarkers for selection of 2nd line target therapies for treatment of resistant tumors
•	Improve efficacy, safety and tolerability of checkpoint inhibitors and develop biomarkers for more precise selection of therapies
•	Define the mode and sequence of therapy administration when combinations are used

- Identify new sub-groups for targeted therapies