Laboratory Investigation (2017) 97, 116–117

INSIDE THE USCAP JOURNALS

doi:10.1038/labinvest.2016.144

The translational pathology of melanoma

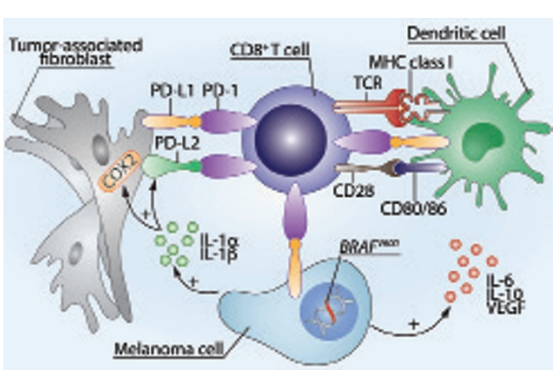
We must, indeed, all hang together or, most assuredly, we shall all hang separately.

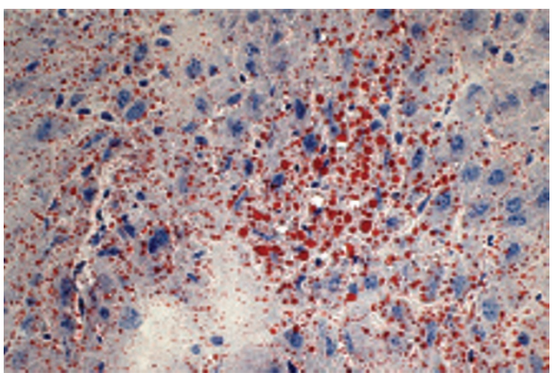
—Benjamin Franklin

With these words, Dr Franklin, arguably one of our most illustrious (and multifaceted) scientists, was not speaking about the study of melanoma. However, melanoma is a threat every bit as virulent as a marauding army, and we in the clinical and scientific communities will ultimately thwart its course only through teamwork and integration of ideas, discovery, and translational application. Through collaboration, data sharing, and highly focused personalized and precise clinical and experimental strategies, enormous strides are increasingly being made in the fight against this aggressive cancer—one capable of lethal metastatic spread from a primary tumor with a volume no greater than that of a peppercorn.

This month's special issue of *Laboratory Investigation*, the first of two, is intended not only to present new and exciting breakthroughs in melanoma investigation but also to provide timely reviews and overviews of salient and related topics. Because all translational research in this critical field ultimately depends on parameters that impact basic diagnostic assessment of primary tumors, Titus *et al* provide insight into how pathologists' interpretation of melanocytic lesions may be influenced by factors extrinsic to the primary tumor. Although somewhat unconventional for an *LI* article, this study serves to remind us that all basic investigation begins and ends with evaluation of pathologically altered tissue from affected patients.

Understanding the root cause of melanoma remains critical, as the best cure is always prevention. The issue





therefore includes cutting-edge papers that focus on ultraviolet radiation (UVR) and non-UVR mutations with respect to their clinicopathological and therapeutic implications (Rawson *et al*), a review of the impact of somatic mutations in the *NF1* gene (Kiuru and Busam), and an overview of the role of kinase fusions in the genesis and pathobiology of spitzoid melanocytic neoplasms (Shalin). Once formed, however, primary melanomas progress from flat, surgically curable lesions to more invasive and tumorigenic ones in which constituent cells acquire the ability to invade dermal lymphatic vessels. Remarkably, the secrets behind this migratory ability—the first dynamic step toward metastasis—remain largely hidden. The ability to detect such events in biopsy specimens is integral not only to studies that will ultimately explain this phenomenon but also to patient follow-up and therapeutic planning, as discussed by Moy *et al*. The mediators of melanoma cell/lymphatic endothelial cell interactions are only beginning to be understood, and the pioneering study by Bastos *et al* focusing on fatty acid synthetase inhibition is a major stride in this direction.

Of course, once metastases have taken hold at distant sites, translational approaches to melanoma require carefully crafted, targeted, and combinatorial therapeutic strategies. Recent therapies taking aim on specific molecular pathways and immune checkpoints have provided reason for guarded optimism. In this issue of *LI*, the crossroads of cancer pathway and immunologic manipulation is highlighted by the timely review by Mandalà *et al*, who examine the immunomodulatory properties of BRAF inhibitors. How melanomas can escape from the therapeutic effects of targeted therapies remains a pressing issue. This critical problem is addressed by Hartman *et al* in terms of the mixed effects of MEK/ERK inhibitors on CD271 melanoma stem cells and relevant mediators, by Hendrix *et al* regarding persistence of Nodal-

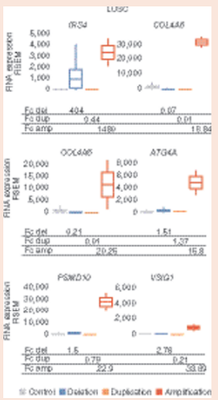
expressing melanoma cells after BRAF inhibition, and by Bresler *et al* concerning apparent induction of resistance genes by melanoma cells after anti-CTLA4 checkpoint blockade. Such novel and necessary studies are direly needed to better understand how our new targeted therapies may be combinatorially modified to target all melanoma cells before escape pathways have time to emerge.

The importance of current investigative and translational approaches to melanoma pathology is further emphasized by two additional papers on melanoma in *LI*'s clinical companion, *Modern Pathology*. In the current issue, Yang *et al* explore the genetic diversity of anorectal melanomas, and in January Saldanha *et al* highlighted the epigenetic marker 5-hydroxymethylcytosine as an independent predictor of melanoma survival.

In the end, we are only at the cusp of understanding and defeating melanoma. However, in the past several years, real progress has been made. Indeed, the trajectory is now promising for exponential advances toward effective translational approaches to melanoma cure. Investigative pathology, closely allied with clinical and diagnostic breakthroughs and refinements, is the linchpin in this pathway that may well inform similarly effective approaches to other forms of human cancer. From our vantage point, which spans between patient and genome and back again, we can now win the battle against melanoma. For the translational pathology of melanoma, in the words of William Osler, "The future is today."

nature.com/pathology

Computational model of enhancer hijacking

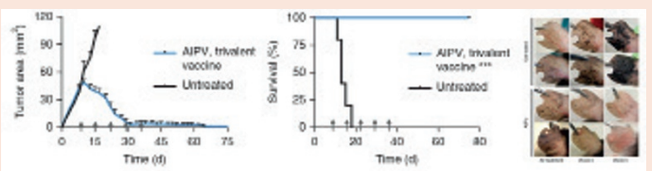


Weischenfeldt *et al* focused on the extent to which recurrent somatic copy-number alterations (SCNAs) exert their influence through rearrangement of *cis*-regulatory elements (CREs). They employed a computational framework termed *cis* expression structural alteration mapping (CESAM) to systematically identify SCNAs mediating gene dysregulation. They observed greater than 10-fold *IRS4* overexpression in 12% of samples and performed validation using RT-qPCR, ChIP-seq, and analysis of active chromatin marks. Recurrent deletions in *cis* were associated with *IRS4* overexpression with *in vivo* evidence for a tumor-promoting role in several cancer types. The group is publishing their findings as the first validated cases of enhancer hijacking in adult solid cancers. They speculate about the use of CESAM in seeking out other enhancer hijacking genes by providing access to otherwise inaccessible regulatory regions of the genome and possible new designs for the assessment of genetic drivers of cancer genomes.

Nature Genetics, published online 21 November 2016; doi:10.1038/ng.3722

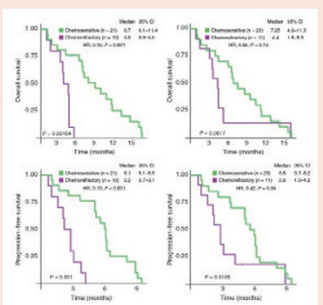
Combination immunotherapy

Advances in immune checkpoint blockade therapeutics have led to dramatic responses in a subset of patients. Using a mouse model of bulky and poorly immunogenic melanoma, Moynihan *et al* saw improved immune cell infiltration into the tumor with substantial remodeling of the tumor microenvironment and enhanced tumor regression using a four-part combination therapy. They call their approach AIPV (A, tumor antigen–specific antibody; I, mouse serum albumin–interleukin-2; P, anti–programmed cell death 1; and V, amphiphile–vaccine). In their melanoma model, tumors grew progressively except in the trivalent vaccine AIPV–treated group, in which they observed clearance of tumor in most animals and a significant increase in overall survival. Although this model demonstrated a proof of concept of harnessing innate immunity against bulky disease in the laboratory, the group acknowledged that the necessary translation to the clinic would present challenges in identifying optimal dosing levels and schedules in human patients, given the complexity of the combined regimen.



Nature Medicine 2016;22:1402–1410; doi:10.1038/nm.4200

Noninvasive tests for genetic profiling of cancer



Carter *et al* investigated the molecular mechanisms that distinguish chemosensitive from chemorefractory small-cell lung cancer (SCLC) by examining copy-number aberrations (CNAs) in circulating tumor cells from pretreatment SCLC blood samples. They generated a CNA-based classifier and used this model to correctly classify 83.3% of their test group cases into the two categories. Notably, when samples were taken at relapse from five patients who had initially been classed as having chemosensitive disease, the patient profiles did not switch to those of a chemorefractory patient, suggesting that the underlying genetic basis for these patients differs from those with *de novo* chemoresistance. Nonetheless, a genetic basis could be identified that directly correlated with clinical outcome. With technical improvements and clinical validation, the results of these minimally invasive tests are potentially quite illuminating. Analysis of additional patient cohorts might suggest additional effective targets to be exploited in a chemoresistant population of cancer patients.

Nature Medicine, published online 21 November 2016; doi:10.1038/nm.4239

Emma Judson contributed to these reviews.