To conquer cancer is first and foremost to understand cancer. Although cancer researchers have solved a significant amount of the cancer puzzle (Fig. 1A) the puzzle as a whole has not been solved and most pieces are themselves puzzles. In the meantime, these puzzle pieces have guided the development of modern cancer therapeutics.

As one example, following the determination that the BRAF kinase in the “kinase networks” piece is frequently activated by the V600E mutation, inhibitors for BRAFV600E were developed and showed remarkable effectiveness for patients with metastatic melanoma containing BRAFV600E, but not for those without BRAFV600E. This exciting success provided the ultimate confirmation of the “driver” role of BRAFV600E. BRAFV600E also exists in many nevi (up to 82%), but most nevi remain as nevi for decades, exhibiting features of cellular senescence. Thus, BRAFV600E by itself is unable to induce melanoma. Furthermore, effective BRAFV600E inhibitors quickly lose their effectiveness. One could therefore ask the question, “How do BRAFV600E inhibitors produce their initial therapeutic benefits?”

Based on current literature, I suggest that oncogenic activation of BRAF in the V600E mutation in the “kinase networks” puzzle piece (Fig. 1A) might first activate the INK4A (also called p16INK4A)-cyclin D1/Cdk4–pRb pathway, the ARF (also called p14ARF)-MDM2/MDM4-p53 (also called TP53) pathway, or both pathways (Fig. 1B). The effectors of these 2 pathways, pRb and p53 respectively, are the 2 major tumor suppressors that together implement the most and the best antitumor mechanisms, such as cell cycle arrest (sometimes to the extreme of cellular senescence), cell death, and emerging mechanisms in cell metabolism, stemness, and epithelial or mesenchymal identity. These effects could prevent BRAFV600E from transforming cells. Ensuing factors, many still undefined, might inactivate pRb, p53, or both (Fig. 1C), allowing tumorigenesis to progress. Inhibition of BRAFV600E in this context halts the mechanisms that inactivate pRb and/or p53, leading to their reactivation (Fig. 1B) to halt the cancer. Combining BRAFV600E inhibitors with inhibitors that target other kinases that interact with BRAFV600E, or with inhibitors that directly reactivate the INK4A-cyclin D1/Cdk4–pRb pathway, the ARF-MDM2/MDM4-p53 pathway, or both pathways, could improve effectiveness and delay or overcome resistance until disease progression to genetic inactivation of pRb and/or p53. When genetically inactivated by DNA sequence deletions, insertions, or mutations in RB1 and TP53 (the genes encoding pRb and p53, respectively), pRb and p53 can no longer be reactivated (Fig. 1D).

The database of TCGA contains data showing frequencies of genetic inactivation of pRb and p53 in various cancer types. For urothelial bladder cancer, genetic inactivation of pRb and p53 co-occurred in 15% of 125 specimens. Prostate cancer progression from adenocarcinoma at primary sites to metastatic cancer at remote sites correlated with an increase in the proportion of cases containing genetic inactivation of both pRb and p53, from 1% to 18%. Thus, a significant number of cancers, especially late-stage cancers, have permanently lost the antitumor mechanisms provided by pRb and p53.

To determine the consequences of genetic inactivation of pRb and p53 in cancer therapy, Zhao et al. used Skp2 deletion to inhibit pRb and p53 double knockout (DKO) tumorigenesis in mouse models. Skp2 is best known as an E3 ubiquitin ligase for p27, and previous studies showed that Skp2 deletion blocked Rb1 (mouse homolog to RB1)-deficient, or Arf−, or Pten-deficient tumorigenesis. Zhao et al. reported that p53 is a transactivator for the promoters of Pirh2 and KPC1 p27 ubiquitin ligases. Consequently, combined deletion of Trp53
Increased p27 protein levels following deletion of Skp2 can relieve cyclin A repression of E2F1 on E2F target promoters, and one of the targets of mir-17-92 is E2F1 mRNA. Could small molecules be designed that produce these effects in cancer cells? Favoring cancer cells is the fact that, although Rb1 and Trp53 deletions are definitive, the additional oncogenic events that lead to DKO tumorigenesis vary and DKO prostate cancer can develop from only 1-2 focal lesions. It is possible that the nature of these additional events varies more widely in human cancer and thus will blunt the mechanisms that we have uncovered in mouse models. In short, will antitumor mechanisms that remain effective when pRb and p53 are genetically inactivated provide the ultimate rationale for cancer therapy? Only search and research will provide the answer.

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Figure 1. Current landscape of cancer therapy. (A) Cancer puzzle pieces as therapeutic targets. Major cancer puzzle pieces are organized according to their cellular location and their interplay as “work-in-progress.” (B–D) Status of pRb and p53 pathway platforms. The first component in the pathways is encoded by an INK4A/ARF hybrid gene CDKN2A. Blue indicates tumor suppressive and red indicates oncogenic. Darker colors indicate stronger functions than lighter colors. Thus, (B) shows an active pRb and p53 platform; (C) shows functionally inactivated pRb and p53; and (D) shows genetically inactivated pRb and p53. See text for a full description of antitumor mechanisms of pRb and p53.
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