That Old Devil Moon

BRUCE A. CHABNER

Department of Medicine, Harvard Medical School and Director of Clinical Research, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA

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The moon continues to capture the imagination of adventure-some souls. In the 1955 classic film, *Picnic*, to the strains of “Moonglow,” Kim Novak enticed a handsome but reckless wanderer, William Holden, into a disastrous one-day romance that ends with his untimely exit from a Kansas town, his new lover in tow. The film graphically depicts the tension between passion and reality. Other themes play through this magnificent film, particularly the oppressive psychology of the town and family. However, the scenario of enticement leading to passionate engagement and unrealized hopes applies not only to romance but also to science and medicine.

Recently, the new president of the MD Anderson Cancer Center, Ronald A. DePinho, announced his own “moon shot” to eradicate and cure eight human tumors, including lung, breast, colon, prostate, melanoma, and ovarian cancer [1]. He is marshaling the forces of his cancer center to eliminate these diseases. The effort is labeled a moon shot after the U.S. expedition to the moon, as launched by President Kennedy in 1961. In this case, the feat will harness the tools of modern molecular biology and genetics to find new targets, personalize therapy, and achieve its goal.

Other prominent American leaders have fixed their attention, imagination, and hopes on the same target, cancer. In 1964, the National Cancer Institute’s director, Frank Rauscher, launched his Special Virus Cancer Program, which aimed to find viruses and develop vaccines. Labeled a biological moon shot by its later critics [2] and criticized for its inefficient use of contract resources, it did lay the groundwork for important advances in molecular medicine, such as the cervical cancer vaccine.

In his last full year in office (1971), Richard Nixon declared the next assault, a War on Cancer [3]. Although some observers interpreted this action as an attempt to divert attention from Watergate and the Vietnam War, the Presi-

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Correspondence: Bruce A. Chabner, M.D., 10 North Grove Street, LRH 214, Boston, MA, 02114, USA. Telephone: 617-724-3200; Fax: 617-643-2683; e-mail: bchabner@partners.org Received September 26, 2012; accepted for publication October 3, 2012; first published online in *The Oncologist Express* on October 15, 2012. ©AlphaMed Press 1083-7159/2012/\$20.00/0 <http://dx.doi.org/10.1634/theoncologist.2012-0392>

dent's decision responded to public passion against the disease, as marshaled by Benno Schmidt and Mary Lasker. The Nixon War on Cancer resulted in the transfer of a key military research facility, Fort Detrick, Maryland, to the National Cancer Institute (NCI), and led to increases in the cancer research budget. It supported the NCI's continued investment in viral oncology, leading to the identification of targets central to our current concept of "precision medicines" and "personalized cancer care." In addition, the War on Cancer supported the development of unique technologies, resources, and facilities. Fort Detrick (now the NCI's national laboratory for cancer research) has played an indispensable role in acquired immunodeficiency virus and cancer drug development, and the initiation of the NCI's efforts in biological therapeutics. However, 40 years later, the war against cancer continues.

Fifteen years after the Nixon announcement (with the cure of lymphomas and the success of adjuvant therapy of breast cancer established), NCI Director Vincent De Vita set a new and more specific goal for NCI: to halve the cancer mortality rate by the year 2000. His goal was based on the passionate belief that widespread application of the drugs and preventive technologies then at hand could profoundly improve cancer outcomes. I was a part of this effort, as director of the Division of Cancer Treatment. Although we fell short of that goal, De Vita rightly forecast a consistent steady decline in mortality for colon, prostate, breast, and lung cancer in the period from 1990 to the present. However, 30 years later, the goal of reducing cancer mortality by 50% has not been met [4].

And, in the final example of goal setting, in 2003, NCI director Andrew Von Eschenbach vowed to end suffering and death due to cancer, and predicted that we would turn the malady into a chronic disease by 2015 [5]. Von Eschenbach's pronouncement was prompted by the early successes of targeted therapy and by expansion of information technology. Unfortunately, that target has not been realized. Although new drugs

for lung, breast, and prostate cancer have produced impressive initial responses, we have failed to cure or control most metastatic disease.

It is clear from the foregoing that any declaration of intent to eradicate cancer is fraught with uncertainty. To DePinho's credit, he did not set a date or timetable for success, and he established no specific milestones for progress. Based on prior experience, one must accept his declaration with caution. MD Anderson will undoubtedly gather unique resources for its assault, but the path from molecular discovery to effective therapy and, even more challenging, effective prevention, will require many additional years of preclinical and clinical effort, and on a scale that no one institution can muster.

As a complex and multifaceted disease, cancer is unlikely to yield to any single scientific conceptual advance. The attractive hypothesis that every tumor has a druggable target has generated great enthusiasm, but it currently fits only a small fraction of human tumors. Mutated and translocated transcription factors, epigenetic changes, DNA repair defects, and other challenging drivers of oncogenesis have proven to be difficult targets for therapeutic intervention. Even the tumors with obviously druggable mutations (activated tyrosine kinases) eventually become resistant to single-agent therapy [6]. The mechanisms of resistance are manifold and complex. Combination therapy that addresses resistance, as for BRAF-driven melanoma, is only in its infancy.

I applaud Dr. DePinho for his passion and his commitment. No doubt we will eventually achieve success, but the journey will be long and difficult, and perhaps not in our lifetime. Vast resources, beyond those of any one institution, and a generous public commitment to cancer research will be required. At present, there is no guarantee that the research effort will be sustained, let alone expanded, as Congress addresses the fiscal cliff and the federal deficit.

Despite the seductive target and the mellifluous music of personalized medicine, cancer remains a devilish opponent.

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