Abstract

Translational medicine has opened the gateway to the era of personalized medicine. No longer a “one size fits all” approach, the treatment of cancer is now based on an understanding of underlying biologic mechanisms and is increasingly being tailored to the molecular specificity of a tumor. Although oncology still functions within broad disease categories, the future will see an increasing shift to treatment based on the characteristics of an individual’s tumor type. Interestingly, one of the first targeted therapies, all-trans retinoic acid in acute promyelocytic leukemia, was first demonstrated at the bedside with a subsequent return to the bench to elucidate its underlying basis. This was a translocation resulting in disruption of the retinoic acid receptor-α gene. Since then, a rigorous translational approach has led to other success stories, such as imatinib and dasatinib in Philadelphia-positive leukemias. With the discovery of novel biologic agents, future challenges lie in the investigation of optimal combinations and the identification of biomarkers that can provide both predictive and prognostic information. Genomics, proteomics, and the application of mathematical modeling are leading the way to biomarker discovery. Further elucidation of the cancer “stem cell hypothesis” will lead to treatment with combinations of agents used to
target both early epigenetic mechanisms and downstream molecular events. With targeted agents that demonstrate increased efficacy and decreased toxicity, we are now approaching cancer as a chronic disease model. Personalized medicine, with a “bench to bedside and back” paradigm is poised to permanently alter the landscape for cancer management.

**Key Words:** Targeted therapy, Translational medicine, Bioinformatics, All-trans retinoic acid, GIST, Imatinib, Dasatinib, Epigenetics, Decitabine, Stem cell hypothesis

**1. INTRODUCTION**

We are in the midst of a revolution in the treatment of cancer. Translational medicine is leading the way into a new era of personalized medicine. Traditionally, there has been a gap between basic science and clinical medicine. Translational medicine fills this gap with a bidirectional approach linking the two. Scientific discovery is taken from the laboratory to the clinical setting, and clinical data are taken back to the laboratory. This model has been successfully adopted to identify targets in the preclinical setting, develop compounds based on these targets, and treat patients in clinical trials. Less acknowledged but just as important is the art of taking clinical observation back to the laboratory to clarify molecular pathways, resistance mechanisms, and genetic alterations.

During the past 20 years, this translational paradigm of “bench to bedside and back again” has enabled rapid progress in the elucidation of complex biologic mechanisms and the development of rational, targeted therapies. Key molecular processes—growth factor binding, signal transduction, gene transcription control, cell cycle checkpoints, apoptosis, angiogenesis—have emerged as potential targets. The development and regulatory approval of drugs such as rituximab, trastuzumab, imatinib, erlotinib, lapatinib, bevacizumab, and cetuximab have provided clinical validation for this molecularly targeted approach. These discoveries have radically changed the way cancer treatment is conceptualized. The historic “one size fits all” approach of treating cancer in the setting of broad tumor categories is being supplanted by the identification of specific targets and molecular subtypes, leading to a personalized approach to treatment based on a patient’s unique tumor characteristics.

Targeted therapy is personalized therapy. To appreciate the novelty and success of the bench to bedside and back paradigm and the exponential growth in the field of translational medicine, it is helpful to contextualize this progress within a larger historical perspective. In the past, cancer treatments evolved from empiric observation and, not infrequently, chance observation. In 1942, the sinking of a U.S. battleship led to the recognition that mustard gas causes profound lymphoid and myeloid suppression. Following this accidental discovery, mustine (the prototype nitrogen mustard) was used to treat non-Hodgkin’s lymphoma (1). Since then, a majority of the more than 200 currently available cancer drugs were identified serendipitously from plants or fungi.

Translational medicine, fueled by the human genome project, has led to a bench to bedside approach to drug discovery. In revealing a vast amount of information about normal and malignant cells, the human genome project has provided a gateway to the current era of molecular medicine. The emerging fields of proteomics and genomics, bioinformatics and systems biology, and nuclear imaging and nanotechnology (among others) are providing the tools to mine and navigate these data. The development of rational drug therapy is now based on an understanding of the molecular genotypes and phenotypes of disease.

The histories behind the development of all-trans retinoic acid (ATRA), imatinib (Gleevec; Novartis, Cambridge, MA, USA), and decitabine (Dacogen; MGI Pharma/SuperGen, Minneapolis, MN, USA) are different versions of the bench to bedside and back