CCR FOCUS

*From the Editor*

# On Innovating and Inspiring the Clinical Trial Enterprise

Our modern clinical trial system in oncology was built in the years since World War II, after the discovery of the activity of nitrogen mustard and methotrexate in leukemia. Subsequently, much has been accomplished to ensure that clinical trials are safe for patients and accurate in their assessments of therapeutic effect. A clinical trial enterprise has been built in oncology—one that compartmentalizes development into phases I, II, and III with requisite endpoints and infrastructure to match. This structure has accounted for much of the progress that has been made in cancer therapy but over time has become a complex and at times difficult structure to navigate. Although there are transformative drugs that will succeed in any clinical trial structure, many cancer drugs are ultimately incremental in nature and require methodical study. With the number of potential targets steadily expanding due to cancer genome sequencing, the number of drugs in development for cancer exceeding 800, the need to develop some drugs in combination with others, the requirement for companion diagnostic development to aid in patient selection, and the accrual rates among patients with cancer fixed at less than 5%, often, it appears that success in drug development is too reliant on good luck. Guided by Guest Editors Eric Rubin and Patricia LoRusso, this *CCR Focus* examines various aspects of drug development—including both recent innovations and ongoing challenges. Lillian Siu and colleagues describe new approaches to clinical trials based on defining mutations in cancer genomes rather than on tissue of origin. Marc Theoret and colleagues outline considerations involved in the use of expansion cohorts in early drug development, with the recent approval of pembrolizumab based on data from such cohorts. Ian Tannock and colleagues take a data-driven approach to ask why phase III trials often do not validate results obtained in phase II. Finally, David Stewart and colleagues highlight regulatory hurdles that they believe encumber drug development. These articles are complemented by an overview that includes the viewpoints of Don Berry and Stuart Bailey on the next generation of clinical trials. This *CCR Focus* is meant to stimulate thought and conversation about how the next-generation clinical trial enterprise should look. And, as with every *CCR Focus*, it is meant to inspire those working in the field, and to interest and inform those outside.

**Susan E. Bates**
Deputy Editor, *CCR Focus*
National Cancer Institute

**See all articles in this *CCR Focus* section, "Innovations to Speed Drug Development."**

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Susan E. Bates

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