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Breast Cancer and Molecular Medicine
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With 134 Figures and 118 Tables
Why should you buy another book on breast cancer? Don’t you already have enough breast cancer books on your shelf? As editors, we have attempted to create a different kind of breast cancer book. Although the typical breast cancer book is written as a compendium of diagnoses and treatments, the focus of this book is on the present and future of breast cancer research and treatment, with an emphasis on translational research. Breast cancer treatment is moving increasingly toward laboratory-based, targeted therapies that are tailored to the individual patient. The treatment of breast cancer, and probably all cancers, will likely soon be practiced in this radically different fashion. The tsunami wave of laboratory and translational research that is already under way will soon alter the management of breast cancer in fundamental ways, and in fact, is already influencing the way in which we think about treating breast cancer patients and performing research.

Research into clinical, laboratory, and translational aspects of breast cancer has improved enormously our ability to treat and cure patients with this disease. Population-based data (for example, from the USA and the UK) document a substantial decrease in the mortality from breast cancer in the last decade, notwithstanding an increase in the incidence of breast cancer detection, attesting to the benefit in human terms from this research. We believe that this downward trend in mortality is only the beginning.

What makes this book unique is that it considers a wide range of relevant and exciting areas of clinical, translational, and basic research for their potential for clinical application today as well as for transforming future breast cancer treatment. If the history of scientific discovery is any guide, then some, but not all, of these research areas will prove valuable for patient care, and the remainder will fall by the wayside. However, no one can predict today which of these research areas will have the most impact on treating patients in the years to come.
The last 25 years of clinical research have been characterized by large, randomized trials that have led to improved outcomes for populations of women. Some of these trials have addressed differing treatment concepts, and others, different regimens of similar therapy. Overviews and meta-analyses have uncovered major trends. However, for any given trial, only some of the patients will derive the benefit from treatment that is nevertheless applied to the overall group of patients. A limitation of comparing large populations of patients is that some subgroups may be too small to be properly evaluated. While such large clinical trials have improved demonstrably the outcome for the overall group, this approach may do so by overtreating some patients while undertreating others.

With the growing recognition of the large heterogeneity of breast cancer patients, breast cancer treatment is becoming increasingly individualized. The observation that each patient is unique, recognized clinically for decades, is now being confirmed by the genetic analysis of individual tumor DNA specimens. The genetic individuality of tumors strongly supports the clinical trend toward increasingly individualized treatment for each patient.

Today, laboratory-based research is expanding, with the potential to translate into clinically valuable improvements. The most basic and elemental processes are understanding cancer genes, how these genes work, the products and mechanisms of altered cellular functions, and the relationship between cancer cells and normal cells. Laboratory research is fueling our understanding of cancer cell biology. With this research come insights into potential targets to exploit and new targeted therapies to employ. Individually designed combinations of therapies will soon become the norm, and currently available antineoplastic treatments (chemotherapeutic, hormonal, biologic, radiotherapeutic, and surgical) will be used more strategically. Today's translational research presages a new era in which therapies may ultimately be tailored to the most elemental basis of the individual tumor in the individual patient.

Historically, classifying patients into broad groups has facilitated the development of treatment guidelines. "Lumping" patients into broad categories of disease (for example, based on nodal positivity, stage, or hormone receptor status) and "splitting" patients based on individual patient and tumor characteristics both play an important role in the conceptual framework for managing breast cancer patients. For example, lumping patients into so-called early-stage disease guides local-regional management of breast-conservation treatment versus mastec-
tomy, whereas lumping patients into so-called locally advanced breast cancer guides the treatment decision toward neoadjuvant chemotherapy. Nonetheless, the paradigm of broadly grouping patients to guide treatment decisions may soon undergo radical change.

Our increasingly sophisticated understanding of breast cancer is forcing us to recognize substantial clinical heterogeneity, even within predefined patient groups, and to reevaluate our concepts of patient management strategies. Thus, splitting or separating the patients into smaller subgroups of patients has become a widely accepted practice, and tailoring treatment in this fashion has emerged as a rational treatment strategy. Translational research has become the driving factor for much of this change in our approach toward treatment strategies. Furthermore, as the basic principles of cancer biology drive translational efforts into more effective clinical treatment strategies, clinical problems are also driving laboratory-based research to solve these problems.

Many examples could be given to demonstrate translational research findings that have already altered clinical practice today. The use of tamoxifen as a hormonal agent represents a major shift in the systemic management of breast cancer patients, and innumerable women have been cured through the use of this very well tolerated drug. However, the most effective clinical use of tamoxifen takes into account the heterogeneity of patient presentations. After research studies demonstrated the importance of estrogen and progesterone receptors, clinicians were able to determine the appropriate subgroup of tumors (hormone receptor positive) that should be treated with adjuvant tamoxifen. In this way, tamoxifen became the first systemic agent used for targeted breast cancer treatment.

Although uncommon, the clinically observed side effects of tamoxifen can potentially be severe, even life-threatening, and have consequently stimulated laboratory research into developing more specific agents with fewer side effects. Two major groups of new agents have been developed: (1) the selective estrogen receptor modulators (SERMs), and (2) the aromatase inhibitors (AIs). SERMs and AIs may have the same, or an even higher, benefit as tamoxifen for preventing recurrence of disease, but with a lower risk of side effects. These agents are also not without side effects, and so even newer agents continue to be developed for clinical testing.

The AIs have been evaluated in several studies and are challenging tamoxifen as the gold standard both for metastatic disease and in the adjuvant setting. The Arimidex, Tamoxifen Alone or in Combination (ATAC) trial demonstrated an improved dis-
ease-free survival (DFS) and toxicity profile for women treated with anastrozole. The National Cancer Institute of Canada MA 17 trial reported an improved DFS for women receiving 5 years of letrozole after completing a 5-year course of tamoxifen, raising the hypothesis that a prolonged duration of more than 5 years of adjuvant hormonal therapy may be beneficial. In the Intergroup Exemestane Study, an improved DFS was found for the combination of tamoxifen followed by exemestane for a total of 5 years compared to tamoxifen alone for 5 years.

The hereditary breast cancer story is another example of a clinical observation driving translational research. In the not too distant past, it was commonly observed that “breast cancer runs in families.” The power of this clinical observation was channeled into the laboratory finding of specific breast cancer genes associated with hereditary breast cancer. To date, two major genes (BRCA1 and BRCA2), as well as other genes, have been associated with an increased risk of developing breast cancer. Several hereditary breast cancer syndromes have been identified, and the potential exists for identifying additional genes responsible for these breast cancer syndromes.

The ability to use rapid and reliable testing to identify women with specific BRCA mutations has promoted the development of improved management strategies for these patients. The available options today for such patients include a number of tailored strategies, such as prophylactic surgery (for example, bilateral oophorectomies or bilateral mastectomies), systemic agents for breast cancer prevention (for example, tamoxifen), or heightened surveillance (for example, breast cancer screening using magnetic resonance imaging, MRI, in addition to conventional mammography).

The impact of research on clinical practice is not limited to systemic therapies. Many research developments have influenced local-regional treatments and their integration with systemic therapies. For example, improved imaging allows for more accurate surgery. MRI has become part of routine clinical practice, as it is complementary to conventional imaging studies. MRI of the breast may have a role in any number of clinical scenarios, such as improving the definition of the tumor volume, monitoring the response to neoadjuvant chemotherapy for locally advanced breast cancer, more accurate staging of the breast for potential candidates for breast-conservation treatment with early stage disease, and differentiating scar from local recurrence in follow-up after breast-conservation treatment.

The integration of computed tomography (CT) and MRI into radiation oncology treatment planning has become routine in
clinical practice. Furthermore, the integration of high-speed computers has facilitated the delivery of targeted radiation treatment that can increase the radiation dose to the tumor (or target) and decrease the dose to normal tissues, with a corresponding reduction in toxicity. The ability to cover the target volume (for example, the intact breast) while omitting critical normal tissues (for example, the heart and coronary vessels) maintains tumor control, but without the late toxicities that were seen in older studies. One can easily envision even further refinements in local-regional treatment that incorporate the ongoing developments in radiologic imaging.

The future of translational research cannot be predicted. Many, but not all, of the promising strategies explored in this textbook will prove clinically valuable in the years to come. While some of these approaches have already reached the clinic and have made a tremendous impact on patient management today, many strategies, although highly promising, remain to show clinical utility. “Bench to bedside” and “bedside to bench” research for breast cancer is an exciting dynamic that has only just begun to yield valuable results.
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