

The Innovative Decade of Molecular Targeted Therapy

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Just a decade ago, only a limited range of therapeutic strategies was available, which targeted molecules responsible for disease development and progression of both malignant and non-malignant diseases. For the treatment of malignant diseases, a number of conventional genotoxic and/or cytotoxic anticancer agents were utilized as a single agent but mostly in combination. However, the effects of such “classical” therapeutic modalities were frequently limited. Similarly for the treatment of autoimmune diseases, which are benign but intractable, corticosteroids and immune suppressants such as cyclosporine A have been widely utilized regardless of disease type or nature. Although such therapeutic strategies have produced substantial clinical effects, they have been largely utilized on the basis of experience, and, indeed, the mechanisms of disease-specific pathogenesis have remained unclear. Even at that earlier time though, innovative therapeutics was envisaged which would aim at specific molecules responsible for disease pathogenesis for improved therapeutic outcomes.

Understanding the pathogenesis and pathophysiology of diseases is, needless to say, essential for the development of effective therapies. It is often mentioned that “recent advances” in the understanding of molecular pathogenesis and molecular techniques facilitated the development of novel molecular targeted therapeutics. However, this has not always been the case. The development of such therapeutics actually involved long and arduous step-by-step work in many fields. For example, splenomegaly and abnormally high leukocyte counts in Chronic Myelogenous Leukemia (CML) patients were first identified in the 1840s, and the Philadelphia (Ph) chromosome was discovered in the 1950s as the hallmark of CML. Next, it was discovered in the 1980s that BCR-ABL1 Tyrosine Kinase (TK) was an aberrant fusion oncoprotein and the product of the Ph chromosome, and finally a small molecule-specific inhibitor of BCR-ABL1 TK, Imatinib Mesylate (IM), was developed and approved for treatment of CML in this century. The clinical efficacy of imatinib for CML was great, with long-term survival of more than ten years, and TK inhibitors have therefore replaced allogeneic stem cell transplantation as the first-line therapy for the majority of CML patients [1]. Moreover, second-generation TK inhibitors such as dasatinib or nilotinib were developed during the past decade to further improve treatment outcomes of CML and to overcome the resistance to IM [2]. This was thus clearly a lengthy process and the result of major efforts by numerous researchers. Once established, however, the success of this therapeutic innovation in molecular targeted therapy for CML has accelerated progress in translational science in various fields, and currently many molecular targeted therapeutics involving small molecules or monoclonal antibodies have been developed and resulted in improved therapeutic outcomes for various malignant and non-malignant diseases. Those therapeutics use various molecular targeted agents such as anti-HER2 agents, anti-EGFR agents, Anti-Angiogenesis (VEGF) agents, monoclonal antibodies for disease-specific cell surface molecules for various solid and hematologic neoplasms, or biologic compounds such as anti-inflammatory cytokine/chemokine agents for autoimmune diseases [3-5].

In this special issue entitled “Clinical Studies of Molecular Targeted Therapies”, several authors have focused on different aspects of the translation of molecular targeted therapies for various diseases. Uchiyama reviews the accumulating evidence for the pathologic roles of soluble factors in the development of inflammatory bowel diseases,

such as Crohn’s disease and ulcerative colitis, which are representative of benign but hard-to-treat diseases, and provides insights into how this knowledge derived from basic science can be translated in to the development of more effective treatment modalities. Kumar focuses on the use of botanicals for the prevention and treatment of prostate cancers. While botanicals have been used in traditional medicine, sometimes since ancient times, many recent studies have provided precise and factual information on how certain botanicals act on the molecules responsible for disease development and progression. As a result, botanicals are currently not given on the basis of experience but on the basis of scientific rationality, and this underlying evidence has led to clinical studies to substantiate the clinical effects [6]. Kumar uses this story as an example of the developmental pathways leading from old to new therapeutic strategies. Yuasa presents and discusses the results of many clinical studies of currently available novel molecular targeted therapies for renal cell cancer and Kobayashi does so for innovative agents for multiple myeloma. They focus in particular on the role of evidence-based medicine showing how the results of clinical studies can be translated into daily practice. Finally, while novel therapies provide new opportunities for improving therapeutic outcomes, they also give rise to an entire range of new clinical questions. For example: How can we make the most of these novel therapeutics? How do we use novel agents in patient management? How can we monitor therapeutic efficacy of novel agents? Are any adverse events associated with new agents? How can we overcome resistance to novel agents? As an example of the implications of such questions, we report on the current principles and new problems involved in the management of CML with TK inhibitors.

The articles in this special issue offer important insights into the development of novel molecular targeted therapies for various diseases and their management. For the development of innovative therapies, it is essential to have access to data on molecular pathogenesis and to the history of and problems associated with existing treatment strategies. For this reason, this special issue contains several representative studies on how new therapies are developed on the basis of fundamental knowledge and how this knowledge can be translated into clinical knowledge for daily practice.

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