Preface

The first hint that the Wnt signaling pathway might be involved in cancer came in the 1980s when one of the integration sites of the Mouse Mammary Tumor Virus (MMTV) was mapped to *Int-1*, later renamed *Wnt-1* for its homology to the *wingless* (*Wg*) *Drosophila* patterning gene. A second provocative link to cancer came in the mid-1990s when *adenomatous polyposis coli* (*APC*), a tumor suppressor gene already strongly associated with hereditary and sporadic colorectal cancer, was identified as a negative regulator of Wnt signaling. In the years that followed, researchers have uncovered many of the molecular details of pathway regulation and function in developmental systems and adult tissues and found a critical role for Wnt signaling in the stem cells of several tissue types. Moreover, Wnt pathway hyperactivation, or dysregulation of specific pathway components, has now been observed in almost 50% of all human cancers. Numerous genetic animal models have been generated and characterized that provide compelling evidence that pathway activation is necessary and sufficient for the pathogenesis of several tumor types. Importantly, these models also provide preclinical tools to test the efficacy of Wnt pathway antagonists in vivo.

Recently, a major focus in the field has been to develop specific and effective Wnt pathway inhibitors, including small molecules and antibodies, for potential clinical use for colorectal cancer and other tumor types. In fact, nearly all levels or components of the pathway have been targeted, including Wnt secretion, ligand binding, β-catenin stabilization, and of course, β-catenin transcriptional activity. While there have been several successes with impressive preclinical data that are currently leading to clinical trials, there remain several questions and concerns in regard to the safety of antagonizing this pathway for cancer treatment. One issue is the essential role of Wnt signaling in the maintenance and self-renewal of normal adult stem cells and the impact of systemic Wnt pathway inhibition on their number and function. Another challenge is the multifunctional nature of some Wnt pathway components. For example, β-catenin is the major effector of Wnt signaling; yet, its localization and activity at the adherens junctions of differentiated epithelial cells are essential for tissue homeostasis. Therefore, strategies to deplete β-catenin levels, rather than solely inhibit its transcriptional activity, may be problematic. A third formidable challenge is the extent by which the Wnt pathway cooperates with other signaling

pathways to exert its biological effects. While this may result in far-reaching effects of Wnt pathway inhibition to cripple tumor cells, it also might lead to the ability of tumor cells to readily circumvent targeting of the Wnt pathway and develop therapy resistance. An additional challenge is that not all subtypes within tumor types demonstrate Wnt pathway activation. Therefore, it is critical to better understand which patient populations are most likely to respond and design clinical trials around these populations so that effectiveness of Wnt-directed therapies can be accurately evaluated. All of these challenges provide opportunities to better understand the nuances of Wnt signaling while moving toward the clinic with Wnt antagonists.

Each of the chapters of this book presents different aspects of Wnt signaling as they apply to translating basic research into Wnt-directed therapies for cancer patients. They are not comprehensive in their scope, but, instead, give a current snapshot of the state of the field, particularly focused on the importance of Wnt signaling in cancer and the approaches that have been taken to target the pathway therapeutically. Our goal was to highlight how far the field has come in these areas as well as underscore the challenges and opportunities that lie ahead in the next phase of translational studies with Wnt pathway inhibitors.

Chicago, IL — Kathleen H. Goss
Los Angeles, CA — Michael Kahn

http://www.springer.com/978-1-4419-8022-9

Targeting the Wnt Pathway in Cancer
Goss, K.H.; Kahn, M. (Eds.)
2011, XI, 240 p., Hardcover
ISBN: 978-1-4419-8022-9