
PREFACE

Building on the foundation of our first (1999) and second (2004) editions of *Methods in Cell Biology: The Zebrafish*, Monte, Len, and I are pleased to continue this Third Edition with a new volume devoted to two rapidly emerging uses of zebrafish in biomedical research: *Disease Models and Chemical Screens*. Seven years ago, we recruited three chapters in these areas as part of *MCB Vol. 76*. Today, our contributors present 20 chapters on the compelling zebrafish models of human diseases that have been developed subsequently and three new chapters on chemical screens! The zebrafish is clearly poised to become a major vertebrate model for *analysis of diseases* and for *screening* for novel therapeutics and chemical modifiers of biological processes *in vivo*.

Part I, *Disease Models*, covers techniques and protocols for creating and studying zebrafish models of major diseases of humans. For example, transgenic models of human leukemias, pancreatic carcinoma, rhabdomyosarcoma, and melanoma, many of which can be fluorescently imaged, are described together with a plethora of experimental methods. Zebrafish von Hippel-Lindau loss-of-function mutant lines have provided a platform for the identification of genetic pathways, modifiers, and interactors involved in VHL-associated neoplasms. Fanconi Anemia, a disease characterized by bone marrow failure, leukemia, squamous cell carcinoma, and gonadal defects, has been modeled in zebrafish and is providing novel insights into vertebrate oocyte development. Mutant zebrafish lines deficient in the function of known tumor suppressor genes have been generated, and tumor intravasation and metastasis are now easily studied in the ghostly transparent *casper* line. Zebrafish deficient in myelination can be produced and analyzed in exquisite detail, and adipose tissues can be visualized for studies of obesity. The signaling pathways and physical forces that regulate the development and emergence of hematopoietic stem cells are amenable to analysis as a consequence of new zebrafish lines and tools. Models of hemorrhagic stroke and lymphangiogenesis now complement those provided by the mouse. Host-microbe interactions, whether pathogenic or beneficial, can be studied in the zebrafish in the context of Koch's postulates, and the temporal segregation of the development of innate and adaptive immunity makes the zebrafish an excellent system for the study of infectious diseases. Major human diseases of the extracellular matrix and of bone have been modeled using both forward and reverse genetic strategies, and the mutants/morphants can be subjected to chemical screens to identify potentially therapeutic agents. Zebrafish models of human ciliopathies have been established in lines with null mutations in intraflagellar transport or basal body genes. Micro RNA-based gene silencing in zebrafish has been exploited to create temporally and spatially controlled haploinsufficiency

phenotypes. Considering the large-scale, albeit not perfect, conservation of vertebrate biological processes, we anticipate that the zebrafish will be used to generate robust models of many other human diseases in the near future.

Part II, Chemical Screens, presents three chapters on high-throughput technologies for the identification of useful small molecules from large chemical libraries. These chapters provide the rationale and stringent requirements that must be met to ensure that meaningful chemical "hits" are obtained, be they intended as potential cancer therapeutics, as psychiatric medicines, or as modifiers of basic developmental processes.

We trust that this thematically new volume of *MCB: The Zebrafish* will excite both seasoned zebrafish investigators and those just adopting the zebrafish model to embrace the system both for fundamental biological research and for applications in biomedicine.

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