YEAST AS TOOL IN CANCER RESEARCH

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FOREWORD

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Yeast has proved to be the most useful single-celled organism for studying the fundamental aspects of cell biology. Resources are now available for yeast that greatly simplify and empower new investigations, like the presence of strains with each gene deleted, each protein tagged and databases on protein–protein interactions, gene regulation, and subcellular protein location. A powerful combination of genetics, cell biology, and biochemistry employed by thousands of yeast researchers has unraveled the complexities of numerous cellular processes from mitosis to secretion and even uncovered new insights into prion diseases and the role of prions in normal biology. These insights have proven, time and again, to foretell the roles of proteins and pathways in human cells.

The collection of articles in this volume explores the use of yeast in pathway analysis and drug discovery. Yeast has, of course, supplied mankind's most ubiquitous drug for thousands of years. In one aspect, the role of yeast in drug discovery is much like the role of yeast in other areas of biology. Yeast offers the power of genetics and a repetoire of resources available in no other organism. Using yeast in the study of drug targets and metabolism can help to make a science of what has been largely an empirical activity. A science of drug discovery would permit rigorous answers to important questions. What is the target of the drug? Is there more than one target and what are the relative affinities? What is the physiological consequence of inactivating a particular protein? Which drug in a panel is the most specific? How many ways can a cell mutate to resistance? What is the consequence of inhibiting two proteins? Which proteins in the cell if inhibited would produce a desired physiological outcome? Are all the proteins in a pathway equivalent targets? Can one identify drugs that alter the location or interactions of proteins without affecting their activity? Each of these questions can be rigorously answered in yeast but not in most other

systems. Questions like these have rarely been answered in the field of drug discovery.

A more challenging question is: Can yeast be made more applicable for the discovery of drugs against human targets? While many human drugs are active in yeast many are not. The lack of effect in yeast can be due to the fact that yeast does not have the targets at all – e.g., cell surface hormone receptors, or because the orthologous protein in yeast is sufficiently different, or that yeast cells have redundant proteins and inhibition of one is masked by the second. However, even if drugs against human targets are active in yeast, the yeast orthologue is likely to be different enough to preclude optimization of drug identification in yeast. One way to solve this problem is by substitution of human orthologues for yeast ones. One could even substitute human transport proteins and drug-metabolizing proteins to further optimize the yeast system.

Moreover, our ultimate interest in drugs is to alter physiology, which is the product not of single proteins but of pathways and networks of proteins acting in concert. The most effective use of yeast would probably result from substituting entire pathways of yeast proteins with their human counterparts. With the aid of reporters that quantitatively reveal the activity of the pathway at different points one could enter a new era of drug discovery that interrogates modulation of the pathway at different sites. Finally, we should think about using the same approach for pathways that do not normally exist in yeast – for example pathways that synthesize hormones. By constructing the pathway in yeast *de novo* with appropriate reporters one could screen for drugs that modulate hormone synthesis and easily localize the target in the pathway. This sounds like fun. I suspect the dough has only begun to rise on what yeast has to offer in the arena of drug discovery.

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INTRODUCTION

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In 1970, Lee Hartwell reported a series of genetic experiments showing that progression through the cell cycle in yeast was amenable to genetic analysis. At about the same time, several investigators, including Michael Resnick and Brian Cox identified the first yeast mutants that were shown to be defective in DNA repair processes. Walt Fangman and his co-workers were characterizing the basics of yeast chromosomes and yeast DNA replication (even though cytogenetics was not practical, and because yeast lack thymidine kinase, pulse labeling of DNA was not possible). Gerry Fink was identifying the many ways a eukaryote regulates gene expression, while Fred Sherman carried out studies on cytochrome c that illuminated translation (and much else). Other investigators were becoming convinced that yeast could shed light on many fundamental processes that were not accessible in multicellular eukaryotes. Since many investigators committed to using yeast as an experimental system, there was also considerable efforts to increase the scope of yeast genetics by developing new genetic tools, which became an effort to develop molecular, biochemical, and cell biological tools. The important tools developed in yeast are too numerous to mention (although the discovery of gene replacement by homologous recombination surely requires note). Contemporary biologists, even those studying "large" eukaryotes, continue to learn from yeast systems.

Despite the impressive roster of accomplishments in basic biology obtained using yeast as a model, there are areas of importance of cancer research where yeast has not been extensively utilized. In addition, many investigators and clinicians working in many areas of cancer research tend not to think of yeast as being relevant to their areas of interest. In some, cases, yeast researchers have not made the appropriate effort to communicate their results to the cancer research community. The goal of this book is to highlight the contributions that yeast systems have made to in a variety of

areas of cancer research. Accordingly, this volume is intentionally directed more to workers outside the "yeast world" and toward investigators interested in cancer. We have requested the authors to highlight areas where yeast-based systems have made contributions not readily accessible with other experimental systems, and to try to communicate clearly to workers who may not be familiar with yeast.

This book is broadly organized into three sections. The first section, including Chapters 1 through 8 highlight areas of biology that are particularly relevant to cancer research. These include studies of DNA metabolism (Chapters 1, 2, and 7), protein localization and trafficking (Chapters 3, 4, and 6), and cell immortalization (Chapter 5). Chapter 8, a discussion of sphingolipids, is relevant both to the biology, and potentially, the development of novel cancer treatments.

The second section, Chapters 9 and 10 describe how yeast can be used to study human p53. These chapters highlight the ability to learn about the function of human oncoproteins using yeast.

The third section is broadly concerned with studying anticancer drugs in yeast. Some of the chapters discuss concerns broadly relevant to drug action (Chapters 11 and 14), while the actions of specific anticancer drugs, such as rapamycins, platinum compounds, and topoisomerase inhibitors are explored in Chapters 13, 15, and 16. Finally, Chapter 12 describes one broad effort to use yeast as a tool for drug discovery.

There are many other areas of interest not included in this volume where yeast systems have made important contributions to cancer research. These areas include important methodologies such as yeast two hybrid, areas of basic biology such as the study of yeast Ras proteins and yeast kinases, and areas of great relevance to anticancer drugs, such as yeast systems of DNA repair. While we hope to include such topics in future volumes, we also felt that there were other superb sources already available for topics such as a general introduction to yeast.

This book would not have been possible without the efforts of Peggy Vandiveer in the Word Processing Center at St. Jude Children's Hospital. Peggy carefully formatted all of the chapters and cheerfully and quickly handled a huge amount of work. Thanks are also due to Jeffrey Berk and Aman Seth in the Nitiss laboratory, who carefully checked all of the chapters and caught many things that might have slipped through. Support for the generation of this book was provided to JLN by the American Lebanese Syrian Associated Charities (ALSAC).