

Kinesins and Cancer

Frank Kozielski
Editor

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Prof. Frank Kozielski, FSB
Chair, Department of Pharmaceutical
and Biological Chemistry
School of Pharmacy
University College London
London, WC1N 1AX, UK

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Preface

The validation of proteins as disease targets is a notoriously difficult and complex task. In this book, we attempt to validate members of the kinesin superfamily as potential targets for drug development in cancer chemotherapy.

The first chapter sets out the groundwork for subsequent chapters by summarising current knowledge and highlighting common principles and features of the kinesin superfamily, focusing mainly on kinesins involved in mitosis and cytokinesis (mitotic kinesins). The following three chapters illustrate the present status of the most advanced kinesin Eg5 in terms of drug development. Chapter 2 describes the development of highly potent and specific Eg5 inhibitors, a range of which are in clinical development, whereas Chap. 3 details the mechanism of these Eg5-targeting drugs. Chapter 4 summarises the outcome of these inhibitors in multiple phase I and II clinical trials. This chapter also explains some of the reasons why clinical success has so far been only moderate, and in addition provides some intriguing ideas about the lessons to be drawn from these trials for the improvement of future clinical trials on Eg5. In the following eight chapters (Chaps. 5, 6, 7, 8, 9, 10, 11 and 12) experts in the motor field attempt to systematically validate or exclude the remaining 15 human mitotic kinesins as potential targets for cancer chemotherapy. By summarising current knowledge on how mitotic kinesins work, the authors provide a balanced opinion about their usefulness as drug targets, taking into account potential undesired side effects.

Surprisingly, a range of mitotic kinesins seem to represent potential novel targets, making them worthwhile starting points for the development of hits as tool compounds pending further validation. However, previously unknown functions may be discovered or redundant pathways revealed, which may exclude some of the kinesins as potential targets. Will this initial assessment of kinesins as potential targets remain valid in the longer term? Only time will tell.

Kinesins are not the only novel prospective targets of the mitotic spindle. Other non-motor spindle proteins are coming to the fore. Chapter 13, on non-kinesin targets, is an attempt to broaden the search for potential targets of the mitotic spindle.

Finally, the last chapter – on neuronal kinesins – attempts to focus attention on multifunctional kinesins, in particular those that play important roles in mitosis and neuronal development. Work on these kinesins will require careful monitoring to avoid unexpected side effects in the central nervous system, though early results suggest that these worries are unfounded.

These are very exciting times for scientists working in the motor field. By applying cutting-edge methodology, the functions of mitotic kinesins are being elaborated and the mechano-chemistry of these molecular machines revealed in astonishing detail. At the same time kinesins are emerging as medically relevant proteins. They may in the future make the leap from potential to validated targets. Very exciting times lie ahead. I hope that this book will contribute to the initial validation of mitotic kinesins as targets for drug development in cancer chemotherapy.

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Frank Kozielski

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Contributors

Ariane Abrieu Université Montpellier, CRBM, Montpellier, France
CNRS UMR 5237, Montpellier, France

Ritu Aneja Department of Biology, Georgia State University, Atlanta, GA, USA

Nahoum G. Anthony Strathclyde Institute of Pharmacy and Biomedical Sciences,
University of Strathclyde, Glasgow, Scotland, UK

Peter W. Baas Department of Neurobiology and Anatomy, Drexel University
College of Medicine, Philadelphia, PA, USA

Ryan D. Baron Department of Molecular and Clinical Cancer Medicine, University
of Liverpool, Liverpool, UK

Francis A. Barr Department of Biochemistry, University of Oxford, Oxford, UK

Giacomo Berretta Strathclyde Institute of Pharmacy and Biomedical Sciences,
University of Strathclyde, Glasgow, Scotland, UK

Fernando Cabral Department of Integrative Biology and Pharmacology,
University of Texas Medical School, Houston, TX, USA

Jared C. Cochran Department of Molecular and Cellular Biochemistry, Indiana
University, Bloomington, IN, USA

Timothy W. Corson Eugene and Marilyn Glick Eye Institute, Departments of
Ophthalmology, Biochemistry and Molecular Biology, and Pharmacology and
Toxicology, and Simon Cancer Center, Indiana University School of Medicine,
Indianapolis, IN, USA

Robert A. Cross Warwick Medical School, Coventry, UK

Julien Espeut Université Montpellier, CRBM, Montpellier, France
CNRS UMR 5237, Montpellier, France

Anutosh Ganguly Department of Microbiology and Infectious Diseases, Snyder Institute, University of Calgary, Calgary, AB, Canada

James A.D. Good Department of Chemistry, Umeå University, Umeå, Sweden
Umeå Centre for Microbial Research, Umeå University, Umeå, Sweden

Silke Hauf Department of Biological Sciences and Virginia Bioinformatics Institute, Virginia Tech, Blacksburg, VA, USA

Olga I. Kahn Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, PA, USA

Simon P. Mackay Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, Scotland, UK

Robert L. Margolis Tumor Initiation and Maintenance Program, Sanford-Burnham Medical Research Institute, La Jolla, CA, USA

Thomas U. Mayer Department of Biology and Konstanz Research School Chemical Biology, University of Konstanz, Konstanz, Germany

Manjari Mazumdar Kimberley Lane, Houston, TX, USA

René H. Medema Division of Cell Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Tom Misteli National Cancer Institute, NIH, Bethesda, MD, USA

Vaishali Pannu Department of Biology, Georgia State University, Atlanta, GA, USA

Padmashree C.G. Rida Department of Biology, Georgia State University, Atlanta, GA, USA

Steven S. Rosenfeld Department of Cancer Biology and Rose Ella Burkhardt Brain Tumor Center, Cleveland Clinic Foundation, Cleveland, OH, USA

Brigitte L. Thériault Campbell Family Cancer Research Institute, Ontario Cancer Institute, Princess Margaret Cancer Centre, Toronto, ON, Canada

Roy G.H.P. van Heesbeen Division of Cell Biology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Kristen J. Verhey Department of Cell and Developmental Biology, University of Michigan Medical School, Ann Arbor, MI, USA

Claire E. Walczak Medical Sciences, Indiana University, Bloomington, IN, USA

Mythili Yenjerla Tumor Initiation and Maintenance Program, Sanford-Burnham Medical Research Institute, La Jolla, CA, USA