



Preface

ויאמר המלך קח-לי חרב
וגרו את הילד החי לשנים

*"And the king said, bring me a sword ...
and divide the living child in two"*

(King Solomon's trial, Hebrew Bible, Kings I, Chap. 3.)

Τόδε περί ἀμάξης ἐμυθεύετο, ὅστις λύσειε τοῦ ζυγοῦ τῆς ἀμάξης τὸν δεσμόν, τοῦτον χρῆναι ἄρξαι τῆς Ἀσίας.... Ἀλέξανδρος δέ...παίσας τὸν ζῆφει διέκοψε τὸν δεσμόν...

"This was the myth about the coach, that whoever would undo the knot on its yoke, he would become the ruler of Asia. Alexander then drew his sword and cut the knot."

(The myth of the Gordian Knot and Alexander the Great in Alexandrou Anabasis Book B, by Arrianos.)

In the above two mottos the **Sword** was instrumental in resolving intriguing problems. In the trial of King Solomon, the wise King revealed who the mother of the living child was. In the cutting of the Gordian Knot, Alexander quickly resolved an ancient problem and marched to his conquests.

How are these mottos related to RNA Silencing? Scholars of RNA silencing also used a **sword** although they termed it *Dicer* and the cutting, *Dicing*. Most RNA silencings are initiated with *Dicing* double-stranded RNA by the *Dicer*. We shall see that these scholars followed the wisdom of King Solomon and made ample use of *Dicing* to study major problems in genetics, in the regulation of gene expression and in the development of eukaryotes.

Scientific revolutions may be sensed in advance by scholars with an exceptional intuition but the *site* where such revolutions take place is frequently a complete surprise. Not all major revolutions in science took place in main towns. Who would have predicted that the revolution in cosmology, initiated by Copernicus, would take place in a tiny town as Frauenburg (then in Poland, thereafter in Eastern Prussia and now called Frombork in Poland)? In genetics, the first revolution, initiated by Gregor Mendel, happened in a modest Augustinian monastery near Brunn, in Moravia. A further revolution, initiated by Barbara McClintock, took place in a very tranquil surrounding: the Cold Spring Harbor Laboratory of the Carnegie Institution of Washington. This latter revolution heralded the *Transposable Elements* and was the subject of my previous book (Galun, 2003). Another department of the Carnegie Institution of Washington (in Baltimore, MD) was the site of a further genetic revolution: the awareness of the profound role of small dsRNA sequences in gene expression, defense against invaders, remodeling chromatin and regulation of development in eukaryotic organisms.

For brevity I shall adhere to the term *RNA Silencing* as the name of this book. But there are several types of RNA sequences that affect gene expression (e.g. small interfering RNA, microRNA). As in the cases of the revolutions initiated by Mendel and McClintock, the *RNA silencing* was also preceded by information that by retrospect could lead to novel molecular-genetic understanding. But the "birth" of this field of endeavor can be traced to one specific publication by Mello and Fire (Fire *et al.*, 1998) that heralded the silencing of RNA.

Although *RNA silencing* is a young field of investigation it has already solved several genetic/biological riddles and has started to be instrumental to further genetic and developmental studies as well

as to lead to practical applications as gene therapy. As in my previous books, *Transgenic Plants* (Galun and Breiman, 1997), *Manufacture of Medical and Health Products by Transgenic Plants* (Galun and Galun, 2001) and the aforementioned book *Transposable Elements* (Galun, 2003), this book is targeted to a wide range of readers. Therefore, some basic subjects that are prerequisites for the understanding of *RNA silencing* will be discussed briefly as a kind of introduction to the main theme of this book. While most of this book is intended for the novice in this field, it also includes an Appendix that deals with the use of gene silencing for gene therapy. This Appendix was added for the benefit of those who are considering using this approach in their investigations. Consequently, the Appendix is written in a manner that will render it useful for such an endeavor.

While writing this book, I have received generous help from many people and I am very grateful for this help. Professor Dan Segal of the Tel Aviv University invested a great deal of efforts to correct my mistakes in the drafts of the chapters on the nematodes and on *Drosophila* and mosquitoes. My wife, Professor Margalith Galun, read parts of the manuscript and made useful remarks. My son, Professor Eithan Galun, not only wrote the Appendix of this book, but also read and corrected parts of the book that deal with the medical aspects.

My gratitude goes also to several colleagues in the Department of Plant Sciences of the Weizmann Institute of Science: Dr Yuval Eshed, Professor Robert Fluhr, Professor Gad Galili and Professor Avraham Levy who provided useful remarks on specific chapters. I owe thanks to Professor Shulamit Michaeli of Bar-Ilan University who read and corrected Chap. 6. I also thank Dr Izhak Bentwich of the Rosetta-Genomics company in Nes-Ziona for reading Chap. 10 and to Professor Aglaia Athanassiadou of the Medical School of the University of Patras, Greece, for the Greek text of the *Myth of the Gordian Knot*.

I appreciate very much the work of the Secretary of our Department, Mrs Renee Grunebaum, who typed and retyped the manuscript and handled the hundreds of references almost daily during many months and with endless patience and for being able to bear with me during my moody moments. Thanks are due to the Graphic Arts

Department of the Weizmann Institute of Science for performing very professional work on the figures of this book.

I acknowledge the outstanding collaboration of the Publisher, Dr K.K. Phua, Chairman of the World Scientific Publishing Co. (WSPC) in Singapore, and Ms Magdalene Ng, senior editor at WSPC, who was instrumental in rendering my draft into a real book.

I acknowledge the permissions to use figures and tables that were granted by the respective publishers. I provided the source below each table or figure and the full citations are listed in the references. These citations should mean that I am grateful for the consents of the respective publishers to use their copyright material in this book.

To Dr Nillie Weinstein I endow my final and very special gratitude. She encouraged me to commence this book and provided continuous support during my writing period. I benefited immensely from her wisdom and knowledge especially but not only in philosophical issues. Dr Weinstein took an active part in the integration of these issues into the book and carefully reviewed the appropriate phrasings. For the above and for additional contributions, she became an inseparable constituent of my endeavor.