Fine-Tuning Life

'In an engaging and personal style, Henshall relates the stories of discovery and insight that have established microRNAs as key players in the cellular economy, conferring robustness and contextual sensitivity to the processes of life. He relates an accessible and enlightening history of the experiments and ideas in this important field, highlighting open questions along the way and the exciting prospects for therapeutic intervention. *Fine-Tuning Life* is a joy to read and will be a crucial resource for biomedical students and anyone interested in the subtle choreography of life and the thinking and practice of those who seek to reveal its logic.'

Kevin J. Mitchell, Ph.D.,
Associate Professor of Genetics and Neuroscience,
Trinity College Dublin

'This book guides the reader along an accessible and lively journey into how the molecular genetic orchestra, essential for all our lives, is conducted across both health and disease. How we have reached this level of understanding is given "life" through considering the major players as people, as well as via their fundamental discoveries.'

John L. Waddington, Professor Emeritus,
RCSI University of Medicine and Health Sciences, Ireland,
and College of Pharmaceutical Sciences, Soochow University, China

'David Henshall's book is bravely aimed at two unrelated reader communities, presenting a real challenge to the author: science, medicine and pharmacology students and professionals who wish to update their know-how in this relatively new field, and naïve readers excited about novel developments in life sciences research. Dr Henshall conquers that challenge by clearly and methodically explaining the underlying scientific concepts to microRNAs' functioning. He presents their discovery, their role in health and disease, and their potential to become novel therapeutic targets. The book explores the difficulties and achievements in microRNA research and their future use in novel therapeutics in a pandemic era where RNA-based therapies have now become realistic. This book is an enlightening read if you wish to learn how a new discovery can lead to realistic pharmacology prospects, and why there are no microRNA-targeted therapeutics in the current market. Recommended most warmly and with no hesitation.'

Hermona Soreq, Ph.D., Professor of Molecular Neuroscience,
The Edmond and Lily Safra Center for Brain Sciences,
The Hebrew University of Jerusalem

'This book finally gives microRNAs the significance (credit) in human genetics they deserve – from their emerging role in the evolution of the human brain all the way to their prospects for the diagnosis and therapy of brain disorders. A must-read for the aspiring biology student and the established scientist alike.'

Professor Dr Gerhard Schratt, Head of Institute for Neuroscience, ETH Zurich

Fine-Tuning Life

A Guide to MicroRNAs, Your Genome's Master Regulators

David C. Henshall
RCSI University of Medicine and Health Sciences

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To Gail, Charlotte and Matthew – the perfectly tuned molecules that matter most to me

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Ode to the MicroRNA

I appeared at the dawn of life.
Unnoticed for so long, lurking among the great genes.
My journey begins: a snip here, a snip there and I'm ready.
I emerge into the cytosolic sea, a cacophony of molecular noise, machines moving everywhere.
I am not distracted; I shall not deviate on my path – argonaute awaits!
We join, a pocket into which I comfortably slip and stretch out.
Now we begin our task, moving effortlessly along our targets, probing gently.
Ah, a message; a good match, but not perfect.
I pause, my pace slowing. I call in support.
My target is growing aware of its fate now, but it is too late. It is a fly caught in my web, soon to be devoured or discarded.
Sometimes I seek adventures far from home, journeying out to distant sites; my reach is far and wide,
Always gentle, but collectively powerful.
Listen. Do you hear? The noise is quieter, the sound exquisite.
I have served my purpose, my genome, my host cell, bringing sharp order to the chaos.
You miss me when I am not there, and suffer if I take over. Better hope things remain steady.
I am a microRNA. My work is molecular diplomacy.
I am the conductor of the molecular orchestra. This is my story.

Acknowledgements

My first and biggest thanks go to my family. The most important thank-you of all. To my wife Gail and my children Charlotte and Matthew: I love you all so much. Thank you for the encouragement to start to write this and the patience to let me finish. I am sorry I miss too much of our lives together with work. It tears my heart. I hope some of the sacrifice and expanse of lost time was worth it.

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This section is an opportunity for me to show my gratitude to colleagues and I have a lot of people to thank. If I miss anyone, I apologise. Since this is my first and perhaps only book, I'm going to take a step back and use the space to thank people who have influenced my research and career.

Let me start with lab members. I have been lucky to find some very smart people who were willing to work for me. Since this is a book about microRNAs, it seems appropriate to begin with some of the people who worked with me in the early days. So thank you to Eva, Tobias and Ray Stallings and his team from whom we borrowed and with whom we shared so much in the early years. Thank you to those who led the microRNA work in the second wave – Cristina, Suzanne, Catherine, Rana, Omar and Mona.

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Edinburgh/the PhD years. John Sharkey, my PhD supervisor at Edinburgh. You taught me many lessons. The importance of getting really good at a few techniques that people would value – how to be an 'expert' at something, and the importance of time and hard work in the lab. I should have thanked you more then and since. I carried your work ethic with me to the USA where you told me I should go if I wanted to get on.

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in those early days when I missed my family. It kept me going. And thank you for helping Gail when she visited me. Do you remember teaching her to drive on the right? Anytime I feel too busy to help someone, I remind myself that you, a head of department at a major university, took time out of your day to help the girlfriend of a lab member learn to drive. That is someone very special.

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Common Terms and Definitions

Aetiology	The cause of the disease
Antimir	An antisense oligonucleotide that targets a microRNA
Argonaute	The protein that holds the active microRNA and brings it to its target
Cluster	A set of microRNAs generated from the same precursor genes, often with overlapping targets and functions
Dendrite	The branched structure extending out from a neurone that bears the synaptic sites that collect incoming signals from other neurones
Dicer	The enzyme that cleaves the pre-microRNA to generate the final form that is passed to the Argonaute protein
Differentiation	The process whereby a cell transitions from dividing towards specialisation
Epileptogenesis	The process by which a normal brain is changed to one that generates spontaneous seizures
Hippocampus	Part of the temporal lobe in the brain, a structure involved in learning, memory and spatial navigation
Knockout	A genetic manipulation in which copies of a gene have been deleted or mutated
Phenotype	The observable characteristics of an organism
siRNA/RNAi	A process for gene silencing triggered by introduction of double-stranded RNAs with perfect complementarity to an mRNA target
Transcript	An RNA, often used as a synonym for mRNA
3' UTR	A region of the mRNA of a protein-coding gene that contains regulatory information and is the position where most microRNAs bind