Preface

The dream of altering genetic expression to alleviate human disease states—gene therapy—has existed from the dawn of the molecular biology era. Early attempts were made with both DNA and RNA as carriers of genetic information, but the inherent instability of RNA compared with DNA attracted by far the larger share of researchers, vectors, protocols, and success stories. Yet DNA, regardless of whether it is introduced by viral or nonviral modalities, carries the potential of integration into the host genome at unintended sites, which can lead to unwelcome and permanent consequences for the patient. Also, there are some outcomes of gene therapy that are best achieved by transient rather than permanent introduction of new genetic information, e.g., lineage conversion of cell fates, genome editing, and activation of the immune system against pathogens or cancer. For these applications, RNA, particularly mRNA, can be preferable to DNA. The past decade has witnessed new discoveries on how exogenous mRNA activates the host cell’s innate immune response to shut down protein synthesis and destroy the RNA, but importantly, there have also been new discoveries on how this can be managed by modifying the structure of mRNA. Progress has also been made on methods to introduce mRNA into cells, to stabilize it in the cell, and to enhance its translational efficiency. New synthetic techniques have been developed that allow for structural features to be built into mRNA which provide investigational tools, such as fluorescence emission, click chemistry, and photochemical crosslinking. Finally, there have been significant advances in the use of synthetic mRNA for protein replacement therapy, immunotherapy against cancer and infectious diseases, creation of pluripotent stem cells from somatic cells, and genome editing. The chapters in this volume present detailed laboratory protocols for (1) synthesis of mRNA with favorable properties, (2) introduction of the synthetic mRNA into a variety of cell types by a variety of techniques, and (3) use of synthetic mRNA to achieve a range of physiological outcomes.

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