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**A**lthough much of the human genome does not encode proteins, recent studies have revealed that the large amount of ‘non-functional’ non-coding RNA (ncRNA) may in fact have key roles in the regulation of gene expression. In our first Review, Wahlestedt discusses the regulatory mechanisms of action of long ncRNA species and their links to various diseases, while assessing the potential of inhibiting long ncRNAs using antisense oligonucleotides to therapeutically upregulate gene expression. Synthetic nucleoside analogues have been in clinical use as anticancer agents for almost 50 years. Dumontet and colleagues discuss the limitations of these existing agents, including side effects and drug resistance, and review new nucleoside and nucleotide analogues that are currently in development for the treatment of viral infections and cancer. Mitochondrial dysfunction has been associated with age-associated acquired diseases, including cancer, neurodegenerative disorders and metabolic diseases, as well as a large number of inherited mitochondrial disorders. Auwerx and colleagues review key pathways involved in the maintenance of mitochondrial function that may be amenable to therapeutic intervention and discuss recent advances in the development of phenotypic screening strategies to identify agents that are capable of modulating mitochondrial activity. Finally, in a Perspective, Kesselheim and Avorn present and discuss the findings of an extensive systematic survey of expert physicians from 15 medical specialties. The survey investigated the views of the physicians on the most transformative drugs in their field over the past 25 years and the key factors influencing their decision, with the aim of informing the ongoing debate about how to effectively catalyse transformative medical innovation.

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