Editorial

Targeting DNA

The drug discovery community is running out of protein targets. A critical assessment of potential drug targets concluded that only 10–15% of the human proteome was “druggable”, in which the term is defined as the intersection of sets of proteins that are both capable of binding “drug-like” molecules and are the product of disease modifying genes [1]. The number of potential viable protein drug targets may therefore be surprisingly small [1,2], so it is essential to consider options for drug discovery that target other biomolecules.

DNA is a fundamentally attractive drug target. The essence of the “antigene” strategy is that it is advantageous to attack drug targets at their source – the level of gene expression [3,4]. A protein drug target is the product of a particular gene. At each stage of progression through the central dogma (DNA makes RNA makes protein), the absolute number of target molecules to be hit by a drug inhibitor increases. A single gene makes multiple copies of mRNA, which in turn are translated to make multiple copies of the target protein. The number of target molecules is amplified at each stage in the process. By targeting the single gene, rather than the numerous resultant protein molecules, drug action should become both more selective and efficient. Antigene agents can be either small molecules or triplex forming oligonucleotides (TFOs) [5–7]. Mukherjee & Vasquez, in this issue, review the latest advances in TFOs. In addition to gene expression, DNA plays a critical role in other cellular processes, such as telomere maintenance [8]. Telomeres provide protection of the ends of chromosomes, and are maintained in part by the enzyme telomerase that replicates the highly repetitive telomeric DNA [9–12].

How the genome might be most effectively targeted is a key question. Twenty-five years ago, Peter Dervan and Claude Hélène articulated the strategy for the design of sequence-specific DNA molecules [3,4,13]. This work set a paradigm that guided investigators for decades. The design strategy rests on a view of standard duplex DNA, as generally described in the classic Watson–Crick structure. The challenge was to discern unique, sequence-specific features of the duplex that might selectively interact with small molecules. The strategy lead to the discovery of a “code” for recognition of duplex DNA grooves by both small molecules [14] or triple helix forming oligonucleotides [15–17].

The realization that DNA is polymorphic and that it adopts a wide variety of secondary and tertiary structures within the genome [18,19] lead to another strategy. Localized unique structures surely play a role in gene expression [10,19–23]. Using small molecules to target such structures represents a promising avenue for drug development, one that is just beginning to be recognized and exploited [10,22,24–28].

Most recently four-stranded quadruplex DNA (G4 DNA) has emerged as a unique and active target. This structure is of special interest because of its high stability under physiological conditions. Quadruplexes are stabilized by guanine quartets and may be formed in guanine-rich DNA or RNA regions; they may be important in human cells for genome stability, transcription, replication, RNA translation, splicing, as well as telomere maintenance. The current issue explores the recognition of DNA G-quadruplexes by proteins or small ligands, using a variety of in silico, biochemical and biophysical methods. Since the original discovery of a quadruplex ligand [29], a number of compounds interacting with G4 DNA have been described in the literature (for a review, [30]). New protocols are presented here to identify new ligands and analyze their binding affinities and selectivities.

Acknowledgments

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References


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