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Review

Discovery and development of the G-rich oligonucleotide AS1411 as a novel treatment for cancer

Paula J. Bates *, Damian A. Laber, Donald M. Miller, Shelia D. Thomas, John O. Trent

Molecular Targets Group, James Graham Brown Cancer Center, Department of Medicine, University of Louisville, 580 S. Preston St., Louisville, Kentucky 40202, USA

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ABSTRACT

Certain guanine-rich (G-rich) DNA and RNA molecules can associate intermolecularly or intramolecularly to form four stranded or "quadruplex" structures, which have unusual biophysical and biological properties. Several synthetic G-rich quadruplex-forming oligodeoxynucleotides have recently been investigated as therapeutic agents for various human diseases. We refer to these biologically active G-rich oligonucleotides as aptamers because their activities arise from binding to protein targets via shape-specific recognition (analogous to antibody–antigen binding). As therapeutic agents, the G-rich aptamers may have some advantages over monoclonal antibodies and other oligonucleotide-based approaches. For example, quadruplex oligonucleotides are non-immunogenic, heat stable and they have increased resistance to serum nucleases and enhanced cellular uptake compared to unstructured sequences. In this review, we describe the characteristics and activities of G-rich oligonucleotides. We also give a personal perspective on the discovery and development of AS1411, an antiproliferative G-rich phosphodiester oligonucleotide that is currently being tested as an anticancer agent in Phase II clinical trials. This molecule functions as an aptamer to nucleolin, a multifunctional protein that is highly expressed by cancer cells, both intracellularly and on the cell surface. Thus, the serendipitous discovery of the G-rich oligonucleotides also led to the identification of nucleolin as a new molecular target for cancer therapy.

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* Corresponding author.
E-mail address: paula.bates@louisville.edu (P.J. Bates).

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Oligonucleotides as therapeutic agents

Since automated DNA synthesizers became widely available in the 1980s, there has been substantial interest in developing synthetic oligonucleotides for use as therapeutic agents (Gleave and Monia, 2005; Duca et al., 2008; Gewirtz, 2007; de Fougerolles et al., 2007; Tomita et al., 2003; Nimjee et al., 2005; Pestourie et al., 2005; Ireson and Kelland, 2006; Krieg, 2008). Initial strategies aimed to prevent translation or transcription of specific viral or cellular genes via sequence-specific hybridization of oligodeoxynucleotides to target mRNA (the antisense approach) or genomic DNA (the antigene or triplex approach) (Gleave and Monia, 2005; Duca et al., 2008). More recently, the phenomenon of RNA interference has garnered much attention and there is considerable excitement about the therapeutic potential of modified double-stranded RNA oligonucleotides (small interfering RNAs or siRNAs) that can specifically knockdown the expression of disease-associated genes (Gewirtz, 2007; de Fougerolles et al., 2007). In addition to these approaches, in which the synthetic oligonucleotide recognizes a specific nucleic acid target via base pairing, several classes of oligonucleotides have been developed to target proteins or small molecules. These include double-stranded DNA oligonucleotides that act as "decoys" for specific transcription factors (Tomita et al., 2003) and aptamer oligonucleotides, which bind to small molecule or proteins by shape-specific recognition (Nimjee et al., 2005; Pestourie et al., 2005; Ireson and Kelland, 2006). Other prospective therapeutic oligonucleotides include those containing immunostimulatory or "CpG" motifs. These molecules act as agonists of toll-like receptor 9 (TLR9) and thereby induce release of various cytokines, making them potentially useful as vaccine adjuvants or in cancer immunotherapy (Krieg, 2008). Some of the strategies for using oligonucleotides as therapeutics are illustrated in Fig. 1.

While many of these strategies demonstrate considerable therapeutic promise, there are two universal problems that may limit the *in vivo* usefulness of oligonucleotide-based medicines. These two critical issues are the susceptibilities of oligonucleotides to degradation by serum or cellular nucleases and their inefficient internalization by cells (Juliano et al., 2008) (although this latter concern may not be applicable to aptamers that target cell surface or extracellular targets). The stability problem has been largely addressed by using oligonucleotides with chemical modifications to the nucleic acid backbone or sugars. However, the increased resistance to nuclease digestion for some of these modified oligonucleotides, especially first generation phosphorothioate analogs, is offset by their increased toxicity and reduced specificity. In cultured cells, the poor uptake of oligonucleotides has been countered by the use of various transfection methods, such as electroporation and complexation with lipids or liposomes, but none of these approaches are easily translatable to *in vivo* use. Several of the hybridization-dependent approaches, including antisense and siRNAs, have now progressed to clinical testing (Gleave and Monia, 2005; de Fougerolles et al., 2007). Early trials using phosphorothioate antisense molecules have indicated significant toxicity and off-target effects of that backbone (Gleave and Monia, 2005), highlighting the need for alternative strategies.

Unusual biological properties of G-rich oligonucleotides

Throughout the history of therapeutic oligonucleotide development, it has become apparent that sequences containing runs of contiguous guanine (G) bases or those that are generally G-rich often have rather distinct biological properties. In the early days of antisense research, several researchers noted (Yaswen et al., 1993; Maltese et al., 1995; White et al., 1996; Burgess et al., 1995; Benimetskaya et al., 1997; Wang et al., 1998; Saijo et al., 1997; Ramanathan et al., 1994a; Ramanathan et al., 1994b; Balasubramanian et al., 1998) that the biological activities of certain oligonucleotides were not due to a true antisense effect, but rather were linked to the presence of contiguous guanines and the propensities of the oligonucleotides to form quadruplex structures containing G-quartets (Fig. 2). Subsequently, a number of groups have described various quadruplex-forming and G-rich oligonucleotides that have biological activities that are not mediated by an antisense mechanism, but are most likely attributable to the protein-binding (aptameric) effects of these oligonucleotides (Scaggiante et al., 1998; Morassutti et al., 1999; Dapas et al., 2003; Scaggiante et al., 2006; Bates et al., 1999; Xu et al., 2001; Dapić et al., 2002; Dapić et al., 2003; McMicken et al., 2003; Girvan et al., 2006; Teng et al., 2007; Tam et al., 1999; Shen et al., 2002; Simonsson and Henriksson, 2002; Anselmet et al., 2002; Akhtar et al., 2002; Cogoi et al., 2004a,b; Filion et al., 2004; 2003; Aoki et al., 2007; Eller et al.,

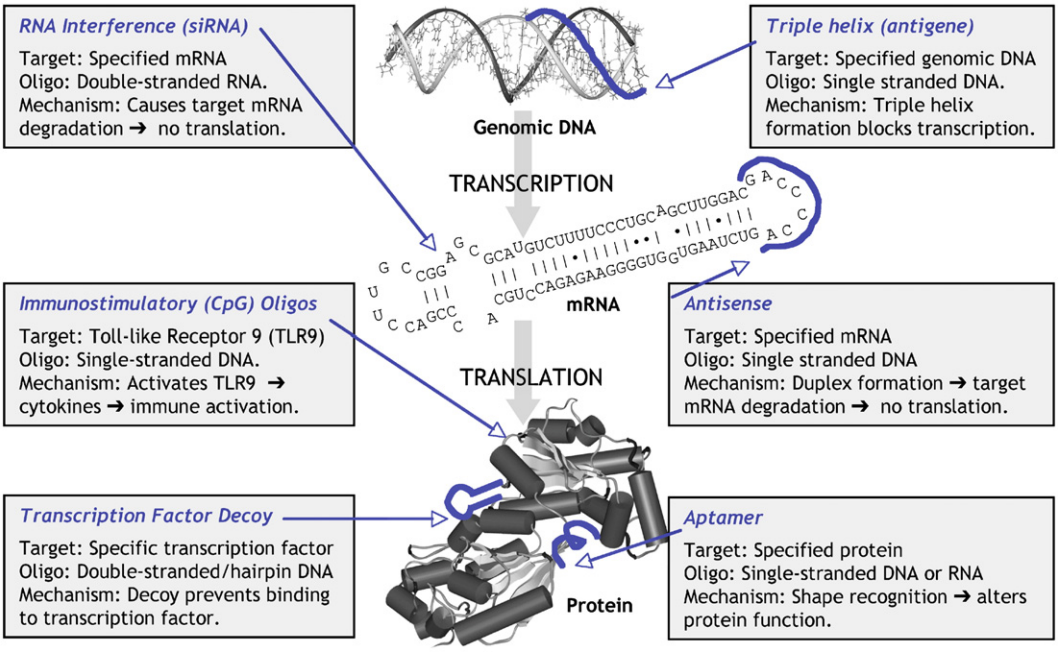

Fig. 1. Strategies for the therapeutic use of oligonucleotides. Cartoon showing different approaches using oligonucleotides (oligos) as targeted therapeutic agents. G-rich oligonucleotides appear to function as aptamers to various proteins. In the case of AS1411, the target protein is believed to be nucleolin.

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