For reprint orders, please contact reprints@future-science.com

Frontiers in nucleic acid-based drug research and development

“This special focus issue showcases cutting-edge original research, commentaries and review articles, discussing the chemistry, design, delivery and therapeutic applications of nucleic acid-based drugs, as well as featuring insightful editorials that shed light on the ‘dark matter’ of the human genome and techniques for the analysis of nucleic acid-based drugs.”

The research and development of therapeutic technologies for modulating gene expression has evolved rapidly in the past decades. In particular, nucleic acid-based drugs (NABDs), including antisense oligonucleotides, ribozymes, siRNA, miRNA, DNazymes and decoys, have been explored extensively for their therapeutic applications. Completion of the human genome program and gradually accumulated expression data by transcriptome analyses has opened up new opportunities for the development of NABDs for targeting gene expressions. Despite the potential broad utility of these agents, the number of NABDs approved by the US FDA is still very limited. Drug delivery challenges, intrinsic toxicity, short therapeutic effects and low efficacy are some of the primary issues that limit the therapeutic potential of these drugs. However, it is a well-accepted notion in the field that with suitable gene target(s) and correct disease settings, NABDs can significantly impact disease progression if the agents are chemically modified appropriately and an efficient delivery strategy is utilized. Indeed, nucleic acid based therapeutic drugs have gained increasing recognition and acceptance by both public health and pharmaceutical communities as is exemplified by the fact that there are currently thousands of NABDs in the drug development pipeline aimed at combating various infectious diseases, cancer and cardiovascular diseases. During the Ebola outbreak crisis in West Africa, one of the two drugs to receive FDA approval for emergency usage for the treatment of Ebola patients was TKM-Ebola, which is a siRNA drug with great efficacy and safety profiles, according to

preclinical studies. In view of the important progress that has been made in the field in recent years, this special focus issue aims to deliver a timely update on significant medicinal chemistry advances in NABD discovery and development.

This special focus issue showcases cutting-edge original research, commentaries and review articles, discussing the chemistry, design, delivery and therapeutic applications of NABDs, as well as featuring insightful editorials that shed light on the ‘dark matter’ of the human genome and techniques for the analysis of NABDs [1–4]. These articles reflect the frontiers currently being explored for a wide variety of cancers, infectious and neuromuscular diseases, at the basic science level, preclinically and clinically. For anticancer therapy, DNazymes had shown promising results in cell culture and in preclinical animal studies, and are beginning to demonstrate success in clinical trials in cancer patients [5]. Next generation of nucleosides, in particular, 4'-eleno-homonucleosides, when phosphorylated by cellular nucleoside kinases, have also been found to exhibit anticancer activity [6]. For antiviral applications, Sizun *et al.* described the 2'-C-a phosphoramidate diester derivative of 2'-C-methylguanosine, known as IDX184, which is designed to inhibit the RNA-dependent RNA polymerase of the hepatitis C virus. IDX184 has been evaluated for the treatment of chronic hepatitis C infection in Phase II clinical trials [7]. Wong's review summarizes the current state of development for NABDs (siRNA, antisense oligonucleotides, dsRNA agonists and others) to combat deadly zoonotic viral diseases, including Ebola and Marburg, and the highly

Lun Quan Sun

Center for Molecular Medicine, Xiangya Hospital, Central South University, Changsha 410008, China

Jonathan P Wong

Author for correspondence:
Defence R&D Canada, Suffield Research Centre, Ralston, Alberta, Canada
Tel.: +1 403 544 4689
Fax: +1 403 544 3388
jonathan.wong@drdc-rddc.gc.ca

**FUTURE
SCIENCE** part of

fsg

pathogenic avian influenza infections [8]. Also featured is a progress report on the modification of nucleoside analogs, specifically carbocyclic nucleosides, which may be potent and have broad-spectrum activity for the treatment or control of viral infections and cancer [9].

With regard to neuromuscular disease therapy, Singh *et al.* describe how antisense oligonucleotides for modulating expression of *SMN* gene represents a promising treatment option for this disease [10]. In a review by Bernado *et al.* the various strategies for manipulating microRNAs activity using a novel class of NABDs is discussed, specifically in relation to studying cardiac biology and therapeutic targets for heart diseases, as well as for hepatitis C and cancer [11].

Last, this special issue describes some of the latest breakthroughs in the enhanced delivery and pharmacokinetics/pharmacodynamics of NABDs. In a review by Lin *et al.* the use of liposome drug delivery systems for improving pharmacokinetics/pharmacodynamics properties of therapeutic nucleotides are discussed, in particular lipid nanoparticles (LNP), which have been found to significantly improve the safety and potency of siRNA drugs in both preclinical and clinical studies [12], and have already shown success in the delivery of siRNAs in Ebola therapy [8,12]. Winkler reviews the modification of NABDs with polyethylene glycol (PEG), which has been found to significantly increase body retention times of these drugs by preventing enzymatic degradation and renal elimination. Various strategies for the PEG attachment and their impacts on pharmacokinetics and gene-silencing efficacies are highlighted in this insightful review [13]. In addition

to PEGylation, Menzi *et al.* and Dirin *et al.*, outlined two other promising strategies to enhance therapeutic effectiveness of NABDs in which the drug is conjugated to functional molecules including polyamines and short basic lysine chains [14,15]. These important strategies can potentially address the significant issues associated with the delivery of NABDs, and therefore enhance stability, cellular uptake and hybridization to gene targets.

The editors would like to express their great appreciation to all the excellent authors of this special issue and for devoting their valuable time to sharing their knowledge and expertise on this important field. We also indebted to Hannah Coaker, the Managing Commissioning Editor of *Future Medical Chemistry*, for her great leadership and tenacity, in developing the concept and in bringing this special issue to fruition. Finally, we would like to thank the editorial board and reviewers for their expertise and input in putting together this issue. It is our earnest hope that it will significantly benefit academicians, students, clinicians, scientists and pharmaceutical and public health leaders.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Guncay A, Yokota T. Antisense oligonucleotide drugs for Duchenne muscular dystrophy: how far have we come and what does the future hold? *Future Med. Chem.* 7(13), 1631–1635 (2015).
- Vocelle D, Chan C, Walton SP. How can novel microscopic approaches shed light on the function of nucleic acid-based drugs? *Future Med. Chem.* 7(13), 1623–1626 (2015).
- Romanelli A. Exploring the dark matter of the human genome using oligonucleotide-based molecules. *Future Med. Chem.* 7(13), 1627–1630 (2015).
- Kurreck J. Application of modified antisense oligonucleotides and siRNAs as antiviral drugs. *Future Med. Chem.* 7(13), 1637–1642 (2015).
- Fu S, Sun LQ. DNzyme-based therapeutics for cancer treatment. *Future Med. Chem.* 7(13), 1701–1707 (2015).
- Yu J, Sahu P, Kim G *et al.* Design, synthesis and cellular metabolism study of 4'-selenonucleosides. *Future Med. Chem.* 7(13), 1643–1655 (2015).
- Sizun G, Pierra C, Peyronnet J *et al.* Design, synthesis, and antiviral evaluation of 2'-C-methyl branched guanosine pronucleotides: the discovery of IDX184, a potent liver-targeted HCV polymerase inhibitor. *Future Med. Chem.* 7(13), 1675–1700 (2015).
- Wong JP. Nucleic acid-based drugs against emerging zoonotic viruses. *Future Med. Chem.* 7(13), 1709–1719 (2015).
- Bessieres B, Chevrier F, Roy V, Agrofoglio LA. Recent progress for the synthesis of selected carbocyclic nucleosides. *Future Med. Chem.* 7(13), 1809–1828 (2015).
- Singh NS, Lee BM, DiDonato CJ, Singh RN. Mechanistic principles of antisense targets for the treatment of spinal muscular atrophy. *Future Med. Chem.* 7(13), 1793–1808 (2015).
- Bernardo BC, Ooi JYY, Lin RCY, McMullen JR. miRNA therapeutics: a new class of drugs with potential therapeutic applications in the heart. *Future Med. Chem.* 7(13), 1771–1792 (2015).
- Lin PJC, Tam YK. Enhanced the pharmacokinetic/pharmacodynamic properties of therapeutic nucleotides using liposomal delivery systems. *Future Med. Chem.* 7(13), 1751–1769 (2015).

- 13 Winkler J. Therapeutic oligonucleotides with polyethylene glycol modifications. *Future Med. Chem.* 7(13), 1721–1731 (2015).
- 14 Menzi M, Lightfoot H, Hal J. Polyamine–oligonucleotide conjugates: a promising direction for nucleic acid tools and therapeutics. *Future Med. Chem.* 7(13), 1733–1749 (2015).
- 15 Dirin M, Urban E, Lachmann B, Noe CR, Winkler J. Concise postsynthetic preparation of oligonucleotide–oligopeptide conjugates through facile disulfide bond formation. *Future Med. Chem.* 7(13), 1657–1673 (2015).