

Golden jubilee of the DNA double helix

Vadim V. Demidov

Center for Advanced Biotechnology, Boston University, 36 Cummington St., 2nd Floor, Boston, MA 02215, USA



'It has not escaped our notice that the specific pairing we have postulated [for DNA] immediately suggests a possible copying mechanism for the genetic material.' J.D. Watson and F.H.C. Crick [1]

'DNA is such an important molecule that it is almost impossible to learn too much about it.' F.H. Crick et al. [2]

'The DNA model of Watson and Crick looks like a diamond as big as the Ritz.' M.D. Frank-Kamenetskii [3]

'Keeping up with the directions and applications of DNA is a never-ending job.' I.E. Alcamo [4]

This month commemorates a significant event in biotechnology*. In April 1953, a short report was published in *Nature* that described the famous double-helical structure of DNA, featuring the specific pairing of nucleobases (the complementarity principle) [1]. This remarkable discovery has stood up well to numerous experimental tests [2,3] and, nine years later, the researchers involved were awarded the Nobel Prize. Such a breakthrough in our understanding of genetic

material dramatically changed every field of life sciences. Importantly, it gave birth to the DNA technology that has transformed many aspects of our lives by forming the basis of the modern pharmacogenomic, bioinformatic and biotechnological revolutions [3–5].

Owing to the seminal findings of Watson and Crick five decades ago, we now have robust hybridization- and PCR-based diagnostics [6], recombinant techniques and recombinant proteins [7], antisense (and, in the future, antigene) drugs [8,9], gene therapy [10], and many more well-established biomolecular technologies, some of which have been reviewed in the pages of *Trends in Biotechnology*. The emerging fields of DNA nanotechnology [11,12], animal and therapeutic cloning [13,14], DNA vaccines [15,16] and DNA computing [17,18] are also rather young offspring of the 50-year-old but still-productive DNA double helix. The recent deciphering of the human and other important genomes must also be mentioned in this context.

The simplicity of the double-helical structure of DNA and the accuracy of interstrand DNA–DNA recognition via specific base pairing brought to life numerous nucleic acid analogs with modified sugar-phosphate backbones [19]. DNA and RNA modifications significantly extended the practical potential of natural DNAs and RNAs, and finally inspired a Danish team, more than decade ago, to design a

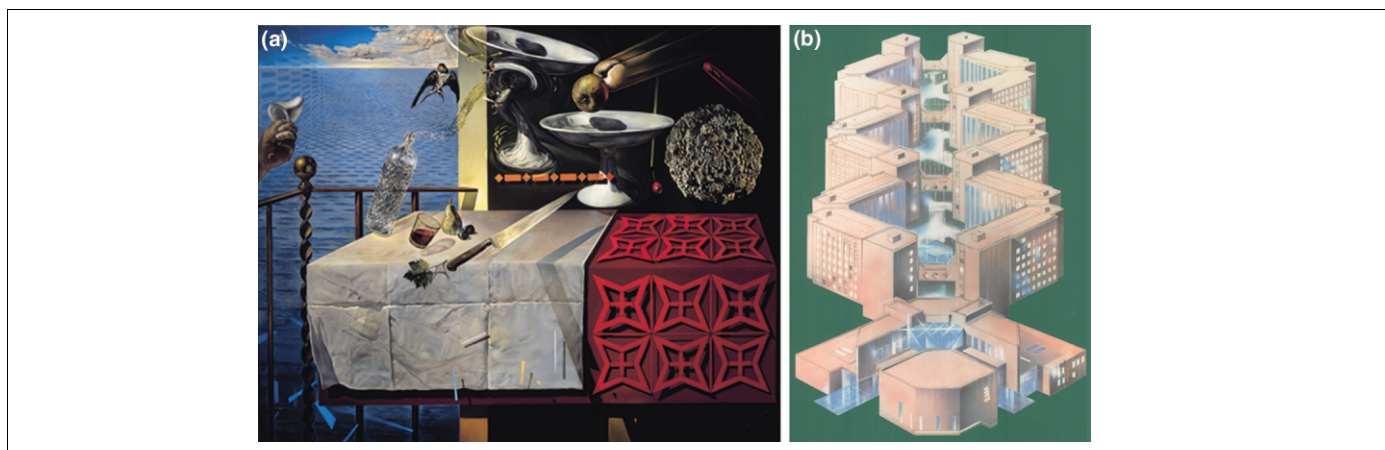


Fig. 1. Inspired by DNA. (a) Salvador Dalí's 'Still Life-Fast Moving (*Nature Morte Vivante*)' painted in 1956, soon after the discovery of the double helix, which had a great influence on the artist. In this drawing one can see several helical objects illustrating the artist's deep belief that spirals of various kinds underlie the very basis of life. Specifically, a bar in the left corner of the fence is drawn in a form of the intertwined double helix. Both the twisting fruit dish in the center and the cauliflower florets on the right also represent spirals. *Nature Morte Vivante (Still Life-Fast Moving)* 1956 Oil on canvas. 49 1/4 × 63 inches. Collection of The Salvador Dali Museum. St. Petersburg, Florida, USA. ©2002 Salvador Dali Museum, Inc. (b) The top view of a unique complex of buildings, the Moscow Institute of Bioorganic Chemistry, designed to resemble the DNA double helix. This institute is one of the world's leading centers in various areas of life sciences, including biotechnology.

Corresponding author: Vadim V. Demidov (vvd@bu.edu).

* Note that while the DNA double helix celebrates its golden jubilee this year, one of its discoverers, James Dewey Watson (born on 6 April 1928 in Chicago, USA), commemorates his diamond jubilee – 75th birthday – the same year to a month.

true DNA mimic – peptide nucleic acid (PNA) – featuring a totally unnatural pseudopeptide backbone [20]. These promising artificial DNA-like molecules opened a completely new page in the field of biotechnological, pharmaceutical and diagnostic applications of nucleobase oligomers [21–23]. In turn, they stimulated the quest for novel analogs and mimics [23–25], which have given new opportunities for directed manipulation of genetic material.

In recent years, significant efforts have been invested in the search for additional, non-Watson-Crick DNA base pairs to advance the stability and recognition specificity of the natural AT and GC base pairs [26–28]. Furthermore, the Watson-Crick recognition principle has been supplemented by the ingenious concept of pseudocomplementarity, which makes it possible to selectively target a wide variety of arbitrary sequences directly within DNA duplexes [29–32]. Successful attempts to expand the genetic code have also been reported [33,34]. This is a promising approach for generating proteins with enhanced properties or even creating ‘synthetic organisms’ with particular functions.

In addition to science and technology, omnipresent DNA penetrates essentially all corners of our everyday life, and has become a cultural icon and even a commodity [35]. The double helix is such a striking symbol that it can be seen everywhere – on commercial posters, artworks (Fig. 1a) and postage stamps, on T-shirts and mugs, and even in the form of perfume bottles and in architecture (Fig. 1b). There is no doubt that the 21st century will be a new era for DNA, the molecular quintessence of life†.

References

- Watson, J.D. and Crick, F.H.C. (1953) Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* 171, 737–738
- Crick, F.H. *et al.* (1979) Is DNA really a double helix? *J. Mol. Biol.* 129, 449–457
- Frank-Kamenetskii, M.D. (1997) *Unraveling DNA: The Most Important Molecule of Life*, Perseus Books
- Alcamo, I.E. (2000) *DNA Technology: The Awesome Skill*, Academic Press
- Trifonov, E.N. (2000) Earliest pages of bioinformatics. *Bioinformatics* 16, 5–9
- Dangler, C.A. ed. (1996) *Nucleic Acid Analysis. Principles and Bioapplications* Wiley-Liss
- Sambrook, J. *et al.* (1989) *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbour Laboratory Press
- Uhlmann, E. (2000) Recent advances in the medicinal chemistry of antisense oligonucleotides. *Curr. Opin. Drug Discov. Dev.* 3, 203–213
- Winters, T.A. (2000) Gene targeted agents: new opportunities for rational drug development. *Curr. Opin. Mol. Ther.* 2, 670–681
- Anderson, W.F. (2000) Gene therapy scores against cancer. *Nat. Med.* 6, 862–863
- Seeman, N.C. and Belcher, A.M. (2002) Emulating biology: building nanostructures from the bottom up. *Proc. Natl. Acad. Sci. U.S.A.* 99, 6451–6455
- Niemeyer, C.M. (2002) Nanotechnology. Tools for the biomolecular engineer. *Science* 297, 62–63
- Tsunoda, Y. and Kato, Y. (2002) Recent progress and problems in animal cloning. *Differentiation* 69, 158–161
- Illmensee, K. (2002) Biotechnology in reproductive medicine. *Differentiation* 69, 167–173
- Caldwell, M. (1997) The dream vaccine. *Discover* (September issue), 84–88
- Taubes, G. (1997) Salvation in a snippet of DNA? *Science* 278, 1711–1714
- Benenson, Y. *et al.* (2001) Programmable and autonomous computing machine made of biomolecules. *Nature* 414, 430–434
- Normile, D. (2002) Molecular computing. DNA-based computer takes aim at genes. *Science* 295, 951
- Uhlmann, E. and Peyman, A. (1990) Antisense oligonucleotides: a new therapeutic principle. *Chem. Rev.* 90, 543–584
- Nielsen, P.E. *et al.* (1991) Sequence selective recognition of DNA by strand displacement with a thymine-substituted polyamide. *Science* 254, 1497–1500
- Ray, A. and Nordén, B. (2000) Peptide nucleic acid (PNA): its medical and biotechnological applications and promise for the future. *FASEB J.* 14, 1041–1060
- Demidov, V.V. (2002) New kids on the block: emerging PNA-based DNA diagnostics. *Expert Rev. Mol. Diagn.* 2, 89–91
- Demidov, V.V. (2002) PNA comes of age: from infancy to maturity. *Drug Discov. Today* 7, 153–155
- Ganesh, K.N. and Nielsen, P.E. (2000) Peptide nucleic acids. Analogs and derivatives. *Curr. Org. Chem.* 4, 916–928
- Braasch, D.A. and Corey, D.R. (2002) Novel antisense and peptide nucleic acid strategies for controlling gene expression. *Biochemistry* 41, 4503–4510
- Horlacher, J. *et al.* (1995) Recognition by viral and cellular DNA polymerases of nucleosides bearing bases with nonstandard hydrogen bonding patterns. *Proc. Natl. Acad. Sci. U.S.A.* 92, 6329–6333
- Morales, J.C. and Kool, E.T. (1998) Efficient replication between non-hydrogen-bonded nucleoside shape analogs. *Nat. Struct. Biol.* 5, 950–954
- Zimmermann, N. *et al.* (2002) A novel silver(I)-mediated DNA base pair. *J. Am. Chem. Soc.* 124, 13684–13685
- Kutyavin, I.V. *et al.* (1996) Oligonucleotides containing 2-aminoadenine and 2-thiothymine act as selectively binding complementary agents. *Biochemistry* 35, 11170–11176
- Lohse, J. *et al.* (1999) Double duplex invasion by peptide nucleic acid: a general principle for sequence-specific targeting of double-stranded DNA. *Proc. Natl. Acad. Sci. U.S.A.* 96, 11804–11808
- Senior, K. (2000) Pseudocomplementary strategy strengthens PNA therapeutic potential. *Drug Discov. Today* 5, 538–540
- Demidov, V.V. *et al.* (2002) Kinetics and mechanism of the DNA double helix invasion by pseudocomplementary peptide nucleic acids. *Proc. Natl. Acad. Sci. U.S.A.* 99, 5953–5958
- Sisido, M. and Hohsaka, T. (2001) Introduction of specialty functions by the position-specific incorporation of nonnatural amino acids into proteins through four-base codon/anticodon pairs. *Appl. Microbiol. Biotechnol.* 57, 274–281
- Wang, L. and Schultz, P.G. (2002) Expanding the genetic code. *Chem. Commun.* 1, 1–11
- Palevitz, B.A. (2002) Awash in DNA news. *The Scientist* 16, 8
- Watson, J.D. (1980) *The Double Helix (A Norton Critical Edition)*, W.W. Norton and Company
- Maddox, B. (2002) *Rosalind Franklin: The Dark Lady of DNA*, Harper Collins Publishers

† For the history of ideas, the chronicle of the discovery of the double helix and biographies of the major figures in this adventure see [36,37].