Drug-design of dinamic drugs antagonists on base of supramolecular self-assembled ensemble from completely substituted oligonucleotides

One of perspective methods of treating a whole number of diseases is considered to be gene therapy. This method is based on an intraorganism introduction of a gene being able either to induce generation of a drug in the organism (if the gene is introduced with the usage of viruses) or inactivate (disable) necessary genes – the application of so-called anticomplementary oligonucleotides. The first type of genetic therapy is successfully applied in practice and quite effective in treating some kinds of leucosis, sickle-cell anemia, and a number of inherent gene diseases. The second type of gene therapy did become so wide spread due to the fact that an inactivating antisense DNA (RNA) is immediately inactivated by nucleases and does not have time to take its effect. Besides, the greater part of such anticomplementary DNA (RNA) is unable to get into a cell. This makes researchers look for ways of penetrating the cell membrane by means of obtaining special plasmids or applying liposomes. It is the second type of genetic therapy, which is the most promising for treating cancer, viral diseases, polyresistant tuberculosis and many other diseases, whose treatment involves inactivation this or that gene. The binding area in such drugs was connected to one of the polynucleotide ends and represented a bis-beta-chloroethylamin derivative or other bivalent binding agent capable of inactivating a necessary gene. If we obtain a completely acidified derivative on all exocyclic amino groups in the polynucleotide structure, it will be able to bind itself complementarily with its non-acidified precursor.

Besides, such a bond will have quite a different character – it will be an ionic bond, but not hydrogen one as between complementary chains in polynucleotides.

In places, where there are only positively charged amino groups in the precursor polynucleotide, there will be negatively charged carboxyl groups in the acidified derivative. Thus the derivative obtained will be complementary to its precursor. This allows us to develop a number of drugs capable of not only irreversible inactivating necessary genes but of being protected from nucleases action.

Unlike drugs with a changed carbohydrate component (for example, to morpholine remains), the double helix formed between the target polynucleotide and drug will be absolutely resistant to cell reparation systems (restrictases, nucleases and polymerases), as in the hybridization process a principle of binding changes: a complementary ionic bond is formed, but not a hydrogen one.

Correspondingly, not a single nucleus enzyme is able to unroll such a double helix and hydrolyze or repair the blocked fragment. In this case inactivation is caused by formation of new ionic bonds between drug carboxyls and target nucleotides amino groups. Such a type of bonds remains is beyond the reach of nucleus enzymes. The main target of modeling remains target gene structure design, determination of quantity of amino groups, which can be acidified, calculation of ingredients amount. Thus, the greater part of molecular modeling tools is unnecessary, but the number of modeled and obtained drugs is unlimited.