Manthan, International Journal, vol. 9, July, 2009, ISSN No. 0974-6331

Nucleic Acid Therapeutics

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Information storage and retrieval, catalytic potential and self replicability are pivotal to qualify an autonomous biomolecule or biomolecular assembly, so much so that earliest living systems might have had nucleic acids as the main or sole constituent. It is not surprising that all expressions in living systems involve nucleic acids at the beginning as well as at the end of a series of steps along a biological pathway triggered by environmental or developmental cues.

Nucleic acids were discovered nearly 150 years ago by a Swiss Clinical Assistant Friederich Meischer as acidic constituent of nuclei of pus cells when the material basis of inheritance and the role of nuclear content in inheritance was not yet clear. Many conditions forming part of the environment in which Friedrich Meischer worked would have inspired him to attach extra importance to pus cell nuclear content. Some important basic lessons can be derived from a study of the then prevalent conditions in scientific laboratories for developing teaching and research programs today.

Friederich Meischer

Nucleic acids recognize their cognate molecules either by Watson-Crick rules for sequence complementarity or via higher order structures assumed by them. Thus nucleic acid markers can be found for most of the states of living systems including disease states. Many of these can be useful drug targets. Also since the nucleic acids-nucleic acid interactions are based on relatively simple rules of complementarity, nucleic acid drugs can be designed to modulate the form or abundance of the target molecules.

Disease can be viewed as a deviation of a living system from its normal physiological and biochemical equilibria characterizing its health or well being. This can often be attributed to change in the quality or quantity of a functional molecule. Alternatively it can be viewed as elevation of undesirable molecules and depletion of desirable molecules. Cause of this change may be either endogenous or may result from an environmental factor or an infectious agent. Any intervention that results in restoration of normal equilibria can be considered as therapy. Like any pair of mutually cognate molecules, a therapeutic molecule recognizes its target via geometric complementarity, charge compatibility, hydrophobicity, group to group interaction, hydrogen bonds, van der Waal's and other weaker interactions. Such molecules can be designed by first visualizing the detailed structure of the target itself and then testing molecules promising the best fitting with it. In many cases structure of molecules can be approximated by modeling for energy-miinimized conformations. As the size of a molecules increases, the number of variables that any such exercise has to take into account increases enormously and one inevitably deploys high power computing. In the absence of precise information on structure one can take a combinatorial approach where a pool of molecules such as would exist in the extract of natural cells and tissues is tested for the presence of any binders by essentially an affinity chromatographic approach. After a good number of target-binding molecules has been selected, those affecting the functionality of the target are screened and tested for

their therapeutic potential. However, if one could foresee binding as I the case of nucleic acid drugs for nucleic acid targets, one can directly harp on testing for therapeutic value of the designed nucleic acid drug. There are many reasons why one looks to nucleic acids as probable targets as well as drugs. Nucleic acids can be used in several forms as drugs e.g., (a) Nucleotide and base analogues, (b) Antisense oligonucleotides, (c) Triple helix-forming oligonucleotides, (d) Spieglemers, (e) Ribozymes, (f) Riboswitches, (g) interfering RNA e.g., siRNA, miRNA and shRNA and (h) RNA aptamers. The basis of target recognition in most cases results from complementarity of the sequence of bases in the target with those in the targeting molecule except for the nucleic acid aptamers which interact with nucleic acid or non-nucleic acid targets on the basis of higher order structure assumed by them. Taking into account the above, one can design a therapeutic nucleic acid molecule to prevent the template function of the target nucleic acids with reference to their replication, transcription, post-transcriptional processing or translation. One can make necessary modifications in the therapeutic molecule to achieve the desired pharmacokinetic properties such as water solubility, half life in the system, specificity, and no or minimal off target effects.

Catalytic RNA can be used to cleave the target molecules or to trans-splice a wild type (normal) sequence of RNA into a mutant RNA thereby correcting the latter. Sometimes a non-nucleic acid regulatory factor for gene expression can be sequestered with the help of nucleic acids assuming a cognate structure. In our research group we are constructing targeted ribozymes against targets like tumor necrosis factor alpha (a drug target for auto-immune disorders like diabetes mellitus or rheumatoid arthritis), and telomerase (a drug target for a majority of cancer types). We are also constructing RNA aptamers binding with chosen ligands known to be of significance in certain disease e.g., calcium and glutathione. We are also trying to develop modified measles viruses that would recognize the affected cells and deliver therapeutic RNA to them. Many antisense oligonucleotides and ribozymes constructed by other research groups are in various phases of clinical trials. The advantages with nucleic acid therapeutics are (a) very high specificity, (b) minimal off-target effect, and (c) possibility of direct or vector-mediated delivery etc. On the other hand the smallest of these molecules will be several thousand Daltons by molecular mass so that it takes a lot more mass as compared to small molecule drugs in order to attain comparable molar abundance. Strident progress is also being made in developing targeted delivery vehicles which partly compensates for the large mass requirement.