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The Aptamers. Whether the Paradigm Works in Therapeutic Applications?

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Aptameric nucleic acids were introduced in early 1990s as a completely new paradigm of the therapeutics. Aptamers are considered as chemical antibodies with comparable affinity along with some extra advantages, being chemically synthesized, non-immunogenic, and extremely low-toxic. Moreover, rational antidote, a complimentary oligonucleotide, provides simple and fast inactivation of the aptamer.

An excitement on this prominent therapeutics was obscured in some extent through high clearance rate and degradability of natural oligonucleotides. DNA and RNA aptamers were extensively modified and/or conjugated to overcome these non-desirable features. New chemical formulations strongly prolonged the lifetime *in vivo* providing additional toxicity and modified tissue distribution.

Several extracellular targets have been successfully inhibited in the therapeutic manner. Most known examples are anti-thrombin (ARC183, NU172) and anti-VEGF (pegaptanib) aptamers. DNA aptamer to thrombin is the first representative of the class. Several related structures with guanine-quadruplex pharmacophore passed preclinical trials and entered clinical ones. Despite of excellent dose-dependent anticoagulant effect, no one of these aptamers has passed all stages of clinical trials.

Up today, pegaptanib is the only one marketed aptamer (FDA approved in 2004). This PEGylated modified RNA aptamer is used to inhibit redundant angiogenesis in retina. The success story hasn't been continued yet.

Why these unique therapeutics are far less successful than antibodies, their protein counterparts? Why hundreds of well-studied aptamers are so long in research and development stages?

Multiple reasons have to be considered. Rather high production cost stimulates extensive modification that is perceived with great caution especially for therapeutics of chronic usage. Aptameric structures are not so stable; great part of them tends to rearrange or slowly aggregate. Conformational changes are often induced simply with salt composition shift, i.e. the preferred structures could be different in and out of the cell. Conformational state could be influenced with target and off-target proteins.

Next complication regards intracellular targets. Generally, nucleic acids in blood, lymph, and outer cell surface have a few recognizing proteins; so it's a rather simple task to gain target specificity. When the aptamer goes in the cell, the specificity becomes of a great challenge. Any aptamer consists of structuring elements (e.g. duplex or G-quadruplex) and recognizing elements (e.g. bulged bases, hinges, loops). Almost all known structural motifs of DNA and RNA are of use in cells having a variety of corresponding proteins, including transcription factors, topoisomerases, telomeric proteins etc. So aptamer specificity in the cell is far less than that *in vitro*, providing potentially additional side-effects.

The multitarget in-cellular therapeutics could be developed shifting the aptamer paradigm from the specific complex formation to recognizing of multiple function-related targets.

Extensive implementation of the aptamers seems to be ultimately related to the extensive academic research on conformational stability of nucleic acids and cellular proteins associated with DNA and RNA. Anyway the aptamer paradigm is to be changed in the near future.

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