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Euro Virology 2020: Potential of the Aptamers to fill therapeutic gaps to fight RNA viruses- Alfredo Berzal Herranz- Institute of Parasitology and Biomedicine

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The current global pandemic caused by SARS-Cov-2 has revealed the lack of an effective therapeutic treatment, among other major deficiencies. This lack of an effective drug to fight it is a common deficiency in dealing with many other infections caused by RNA viruses, e.g. HIV, HCV, SARS, and Dengue, Zika or Ebola viruses, among others. In addition to the information that encodes the viral proteins, RNA genomes carry all other information required for the successful completion of the viral cycle. It includes the information required to efficiently sequester and utilize the cellular machinery and all the information involved in the regulation of the essential viral processes. To bear all the information RNA viruses have developed different molecular strategies to compact it in different levels of coding within the RNA genomes. Thus, the nucleotide sequence stores essential information in highly conserved structural RNA domains composed of discrete structural units. The different structural genomic RNA domains play essential functions, and the preservation of their structure is essential for their proper functioning. Therefore, interfering with the activity of these essential domains, by competing the interactions they are involved in or by modifying their structure, offers an excellent scenario for fighting infections caused by RNA viruses. It represents a clear alternative to the traditional therapeutic strategies aimed to target viral proteins. Aptamers are short oligonucleotides that efficiently bind to a specific target molecule. The recognition of their target strictly depends on the conformational distribution of specific functional groups in the global structure of the substrate molecule. Therefore, aptamers offer a potential means for the development of efficient therapeutic drugs recognizing specific structural features of the viral RNA genome. Numerous studies have reported the potential of aptamers to act as efficient drugs against a variety of RNA viruses being HIV and HCV some of the favorite targets. We have demonstrated that RNA aptamers targeting different essential structural elements of the HIV and HCV RNA genomes efficiently inhibited their replication, reaching up to 85 and 95% inhibition rates, respectively. These results and those from other authors indicate the potential of the aptamers to fill therapeutic gaps in the fight against RNA viruses.

Hepatitis C infection (HCV) contains a (+) ssRNA genome with profoundly monitored auxiliary, useful RNA areas, a considerable lot of them with obscure jobs for the consecution of the viral cycle. Such genomic spaces are competitor restorative targets. This investigation reports the practical portrayal of a gathering of aptamers focusing on the cis-acting replication component (CRE) of the HCV genome, a significant accomplice for viral replication and furthermore associated with the guideline of protein blend. Methods: Forty-four aptamers were tested for his or her ability to interfere with viral RNA synthesis during a subgenomic replicon system. Some of the foremost efficient inhibitors were further evaluated for his or her potential to affect the recruitment of the HCV RNA-dependent RNA polymerase (NS5B) and therefore the viral translation in cell culture. Results: Four aptamers developed as strong inhibitors of HCV replication by direct collaboration with utilitarian RNA areas of the CRE, yielding a reduction inside the HCV RNA levels above 90%. Concomitantly, one among them also induced a big increase in viral translation (>50%). The three outstanding aptamers proficiently contended with the official of the NS5B protein to the CRE. Ends: Present discoveries affirm the capability of the CRE as an enemy of HCV target and bolster the use of aptamers as sub-atomic devices for researching the usefulness of RNA spaces in viral genomes. Aptamers are confined from a SELEX (Systematic Evolution of Ligands by Exponential advancement) process, which comprises on iterative arrangements of union, authoritative, positive choice, and intensification ventures over a randomized oligonucleotide pool. The resulting population is enriched in those molecules ready to bind to the specified target molecule. The exceptionally powerful collapsing of nucleic acids is that the way to know the exact and productive connection of aptamers to their related objective, in this manner showing the adaptability and flexibility of nucleic acids. Aptamers-mediated inhibition is directly associated with their biochemical features, like their three-dimensional folding and binding affinity to their target. Therefore, further efforts were focused on analyzing those properties.

Aptamers P6-89, P6-96, P6-103, and P7-49 contain sequence motifs complementary to functional RNA domains that are involved in the regulation of HCV translation, such as the 5BSL3.2 and the stem-loop containing the stop codon. This observation led us to review their role on viral protein synthesis in cell culture translation assays.

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