5th International Electronic Conference on Medicinal Chemistry
1-30 November 2019
chaired by Dr. Jean Jacques Vanden Eynde
sponsored by pharmaceuticals

RNA aptamers: antiviral drugs of the future

Alfredo Berzal-Herranz [1,*], Cristina Romero-López

[1] Instituto de Parasitología y Biomedicina "López-Neyra", IPBLN-CSIC PTS Granada. Av del Conocimiento 17, 18016 Granada, Spain

* Corresponding author: aberzalh@ipb.csic.es

Aptamers : RNA or DNA oligonucleotides able to bind specifically and with high affinity to a target molecule

Aptamer

The term Aptamer comes from the Greek voice *haptein* – to bind to

Jack W Szostak

Nature **346**, 818-822 (30 August 1990) | doi:10.1038/346818a0; Accepted

In vitro selection of RNA molecules that bind specific ligands

Andrew D. Ellington & Jack W. Szostak*

1. Department of Molecular Biology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA
2. * To whom correspondence should be addressed. 818

Subpopulations of RNA molecules that bind specifically to a variety of organic dyes have been isolated from a population of random sequence RNA molecules. Roughly one in 10^{10} random sequence RNA molecules folds in such a way as to create a specific binding site for small ligands.

Top

Systematic Evolution of Ligands by Exponential Enrichment: RNA Ligands to Bacteriophage T4 DNA Polymerase

Craig Tuerk; Larry Gold

Science, New Series, Vol. 249, No. 4968 (Aug. 3, 1990), 505-510.

Stable URL:
http://links.jstor.org/sici?sici=0036-8075%2819900803%293%3A249%3A4968%3C505%3ASEOLBE%3E2.0.CO%3B2-I

Science is currently published by American Association for the Advancement of Science.

The authors are in the Department of Molecular, Cellular, Developmental Biology, University of Colorado, Boulder, CO 80309.

SELEX

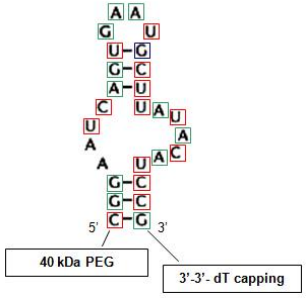
Systematic **E**volution of **L**igands by **EX**ponential enrichment.

Larry Gold

MACUGEN®

Active moleule is Pegaptanib (a *pegylated anti-VEGF RNA aptamer*)

Indicated for the treatment of the Wet age-related macular degeneration



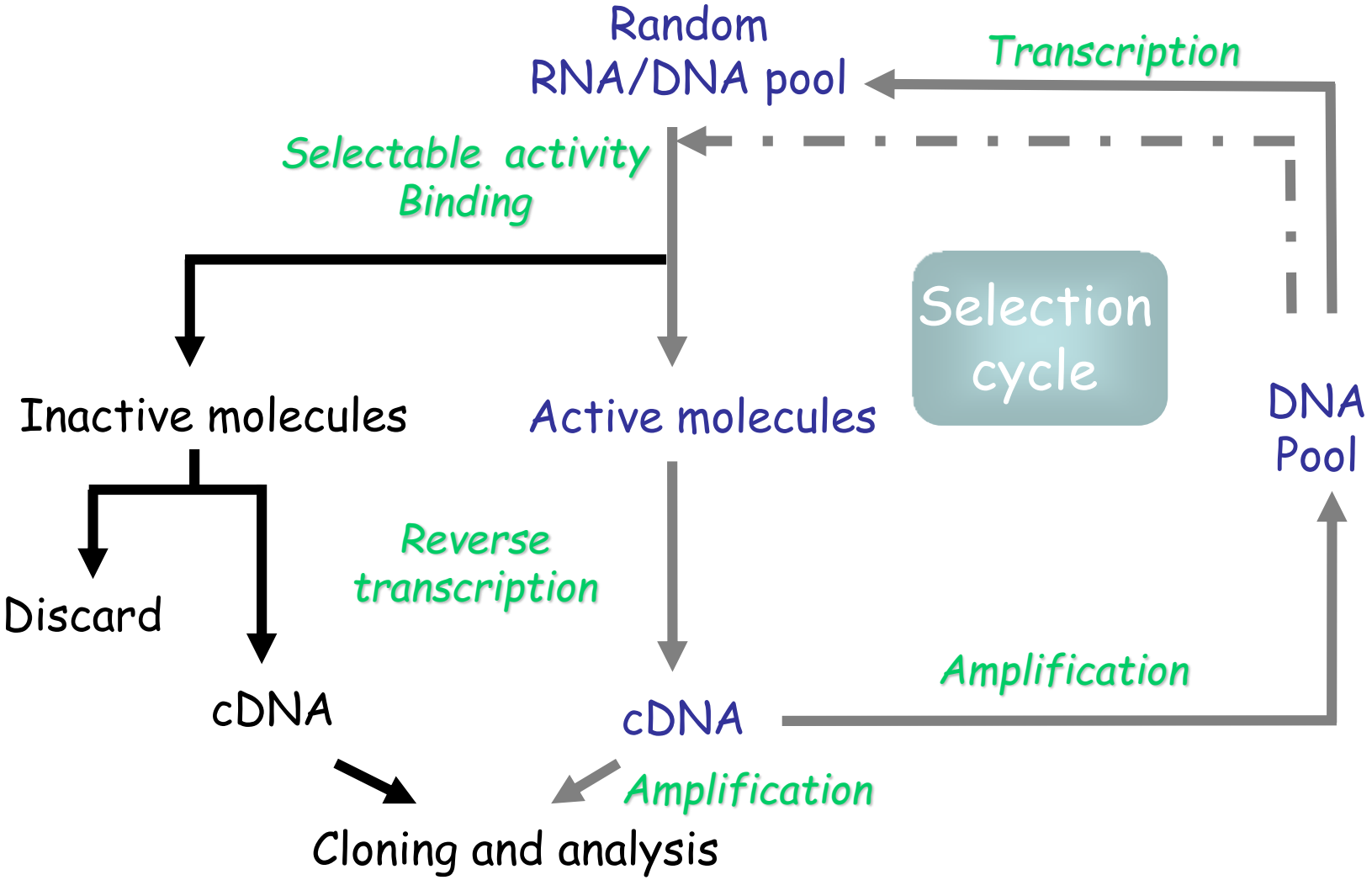
Aprobed by the FDA (Decembre 2004)

Aptamer's targets

Ions
Nucleotides
Aminoacids
Organic compounds
Peptides
Proteins
Nucleic Acids
Virus
Cell organelles
Eukaryotic cells…

Aptamers selection scheme SELEX

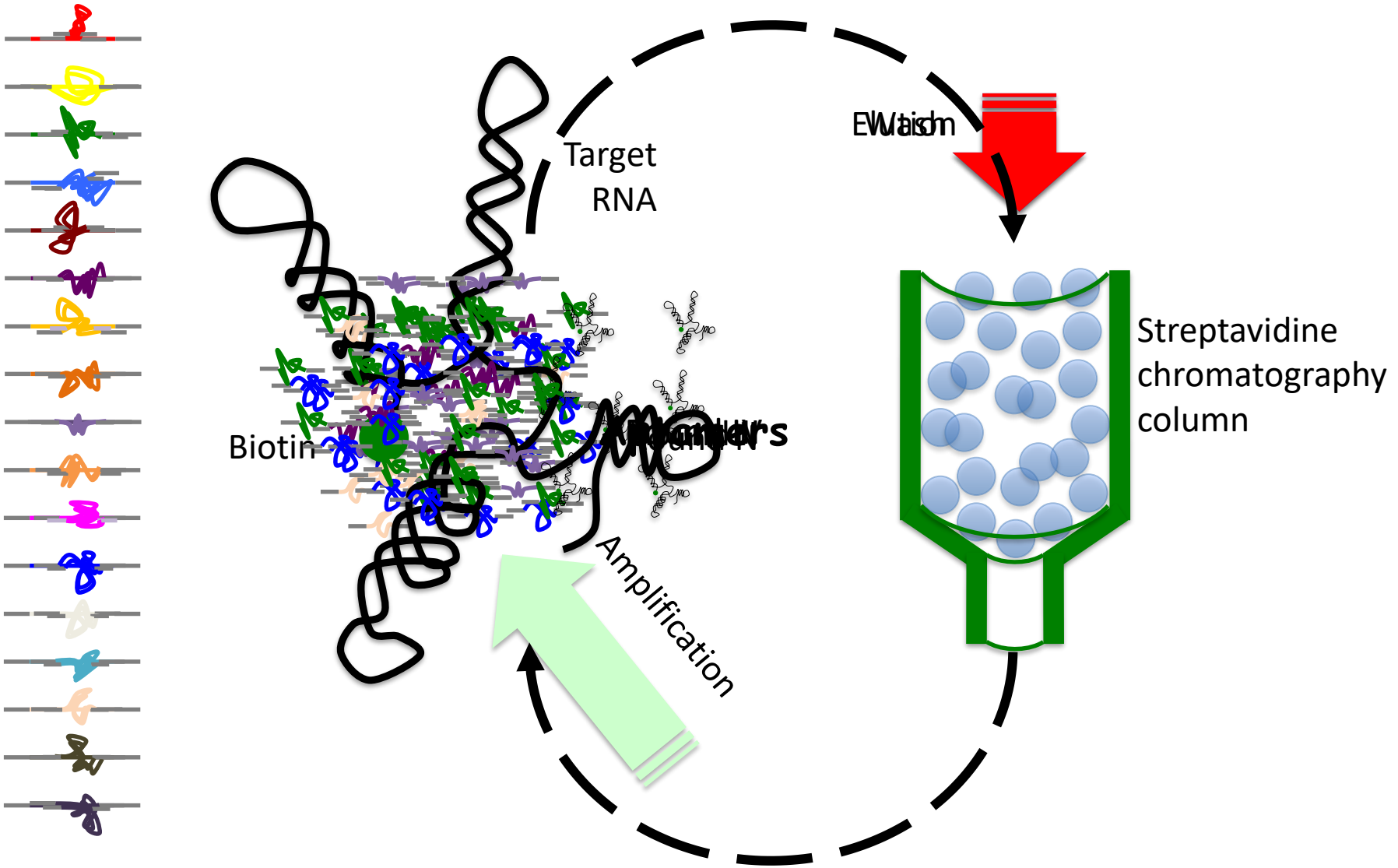
(Systematic Evolution of Ligands by EXponential enrichment)



Aptamer's targets

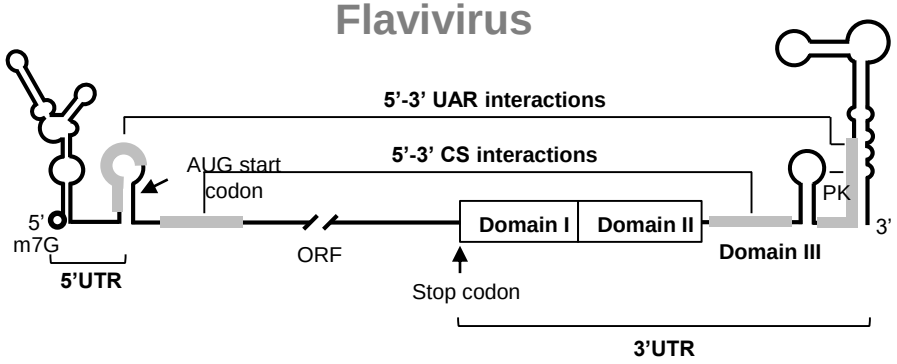
Ions
Nucleotides
Aminoacids
Organic compounds
Peptides
Proteins
Nucleic Acids 
Virus
Cell organelles
Eukaryotic cells…

Sistematic Evolution of Ligands by Exponential enrichment (SELEX)

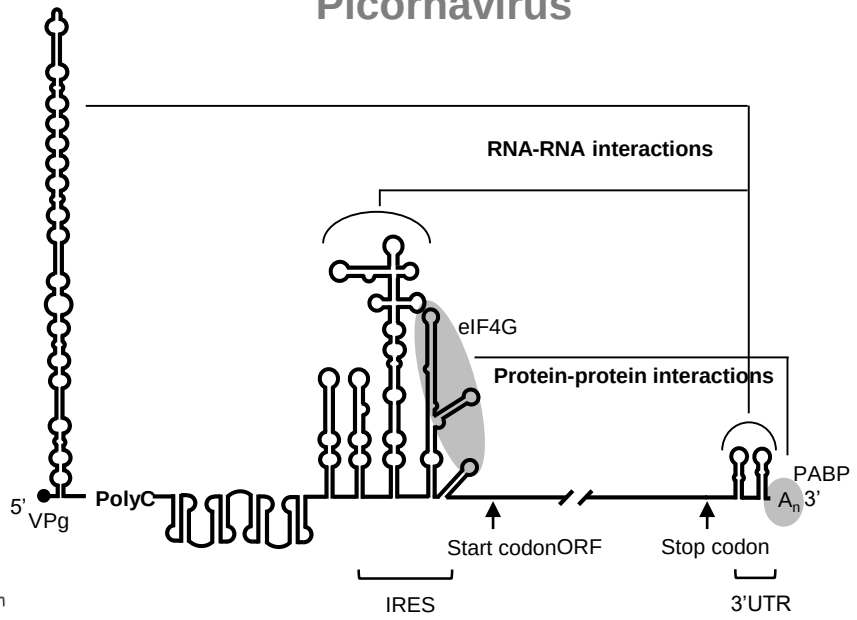


Viral RNA genomes

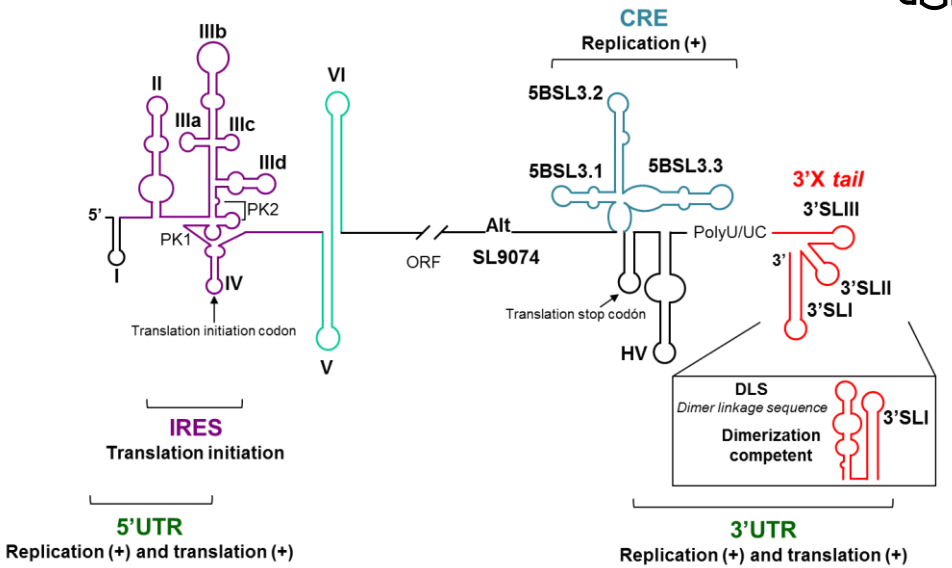
Flavivirus



Picornavirus



Hepacivirus



AIDS

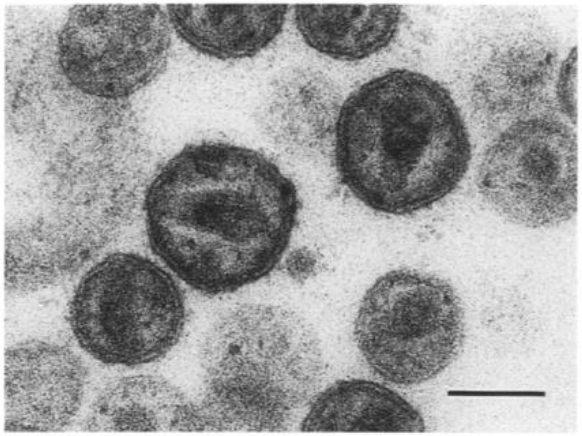


Fig. 4. HIV-1 particle obtained by conventional ultrathin sectioning. The projections on the virions are barely visible. Scale bar indicates 100 nm (Goto *et al.*, 1994).

HIV-1

Cellular and viral proteins

cellular tRNA

Polyadenylacion machinery

VIRUS

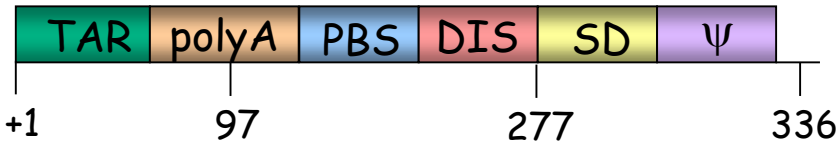
Envelope

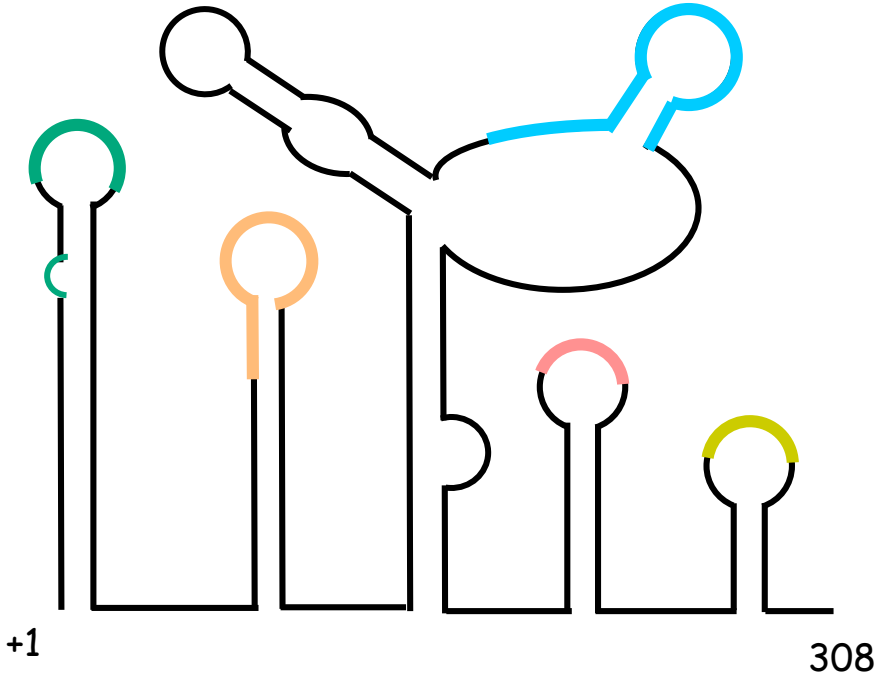
Capside

RNA genome

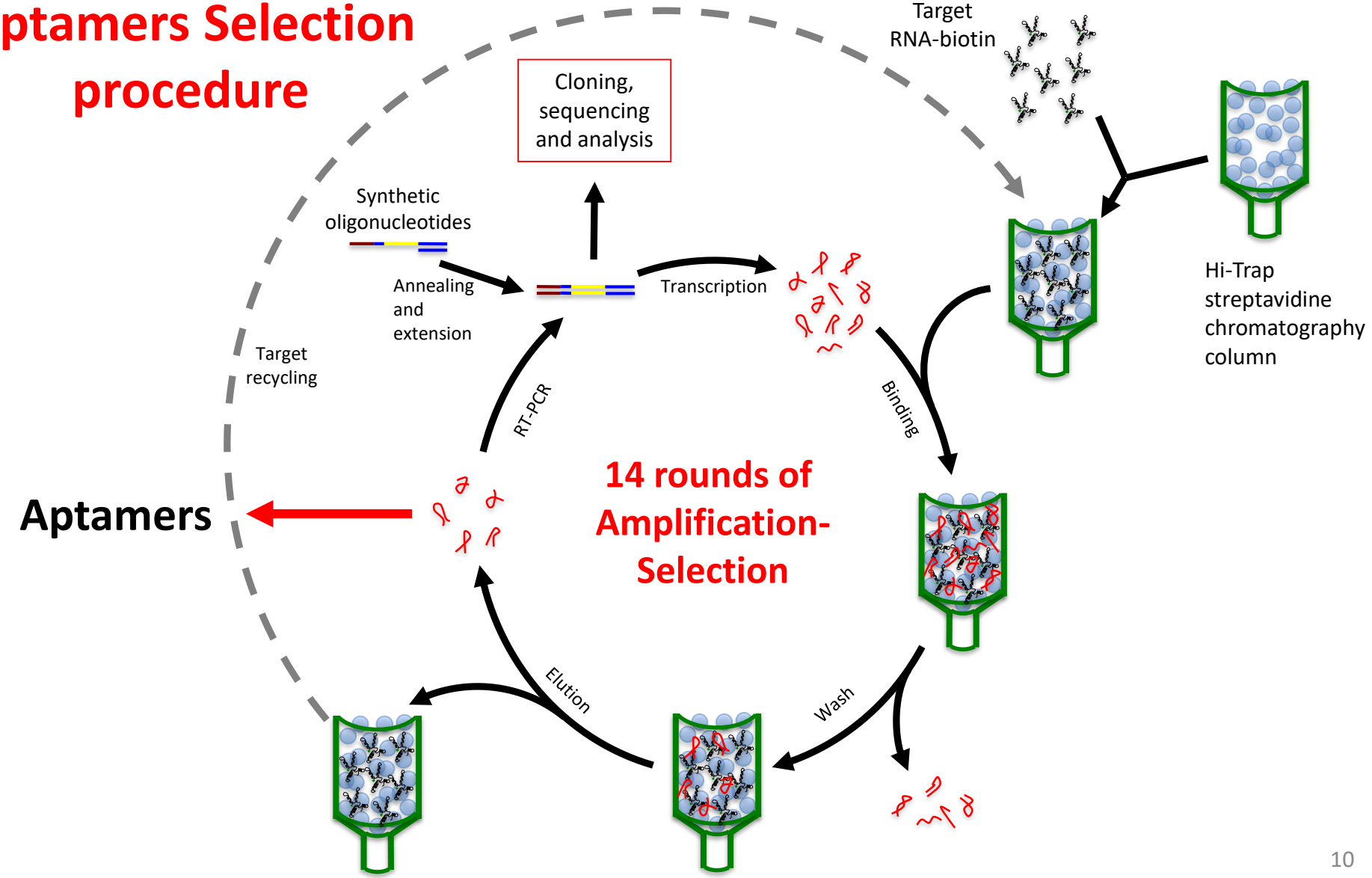
Viral protein

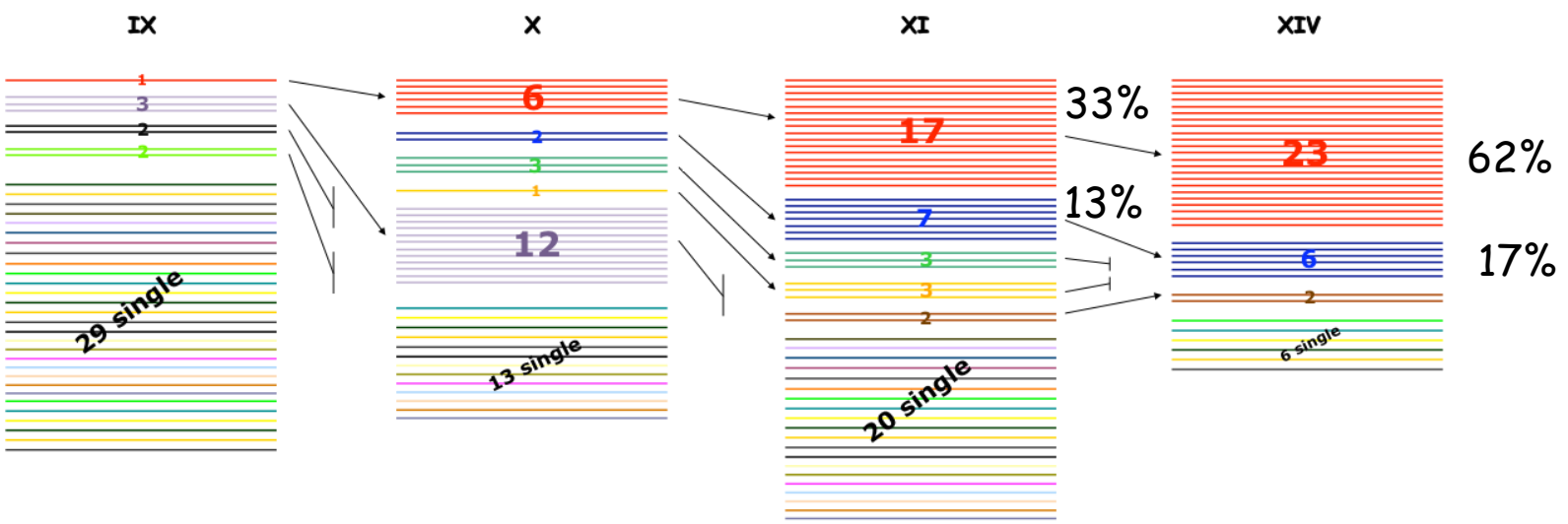
5’ UTR HIV

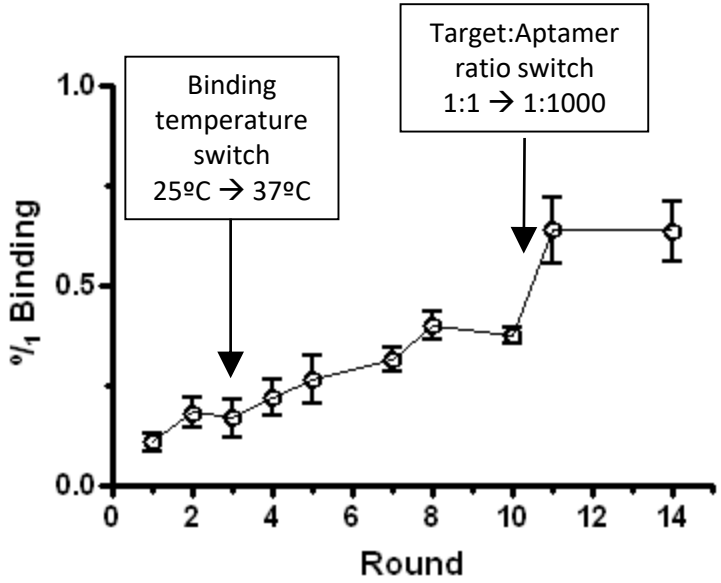




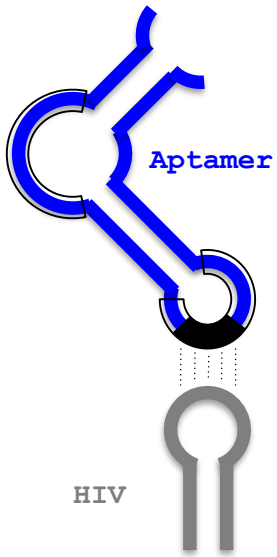
Aptamers Selection procedure





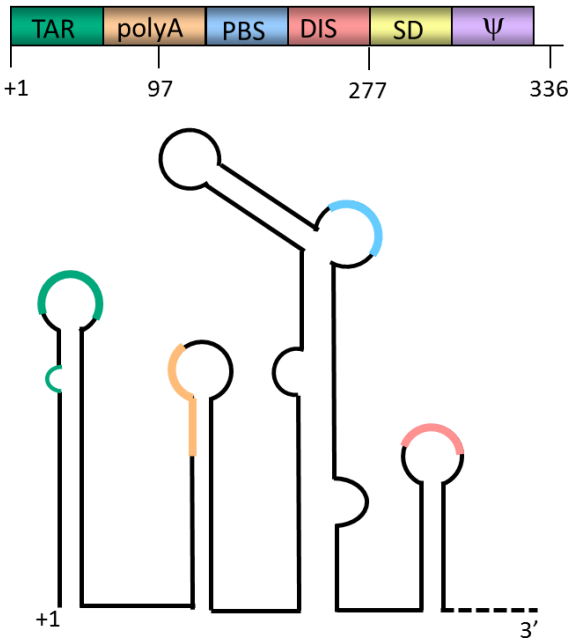


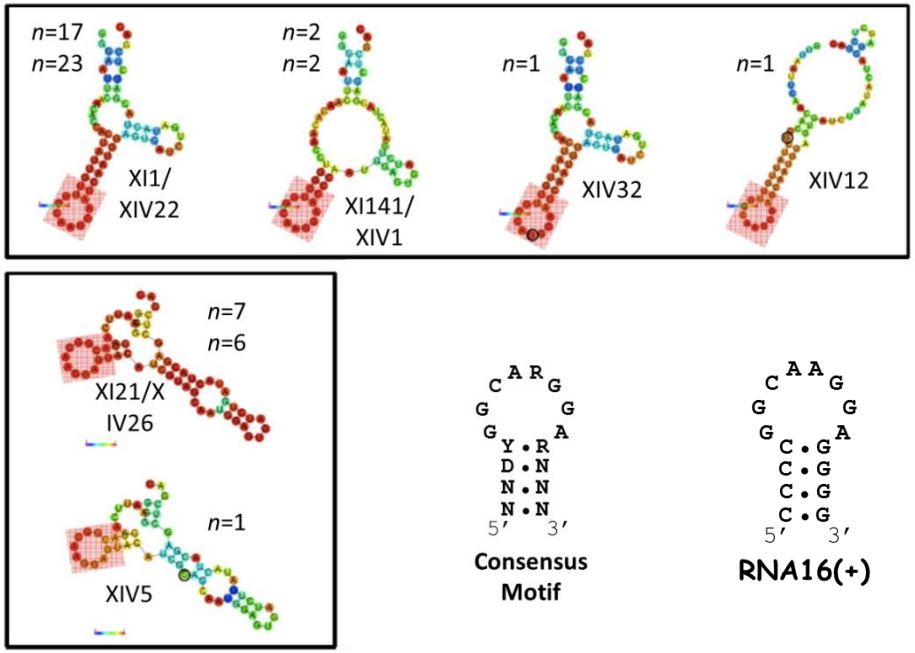
Progression of the selection process



x 23	XIV22	GGGAAUUCAACACCACUAUUGUUGGCAAGGAAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI1	x 17	-
x 6	XIV26	GGGAAUUCAAGUACGGCAAGGAGUACAUCGUAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI21	x 7	-
		GGGAAUUCAAGUACGGCAAGGAGUACAUCGUAGUAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI23	x 3	
x 2	XIV1	GGGAAUUCAACACAACCUGGGUGGCAAGGAACCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI141	x 2	
	XIV12	GGGAAUUCAACACCGCUAUUGUUGGCAAGGAAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC			
		GGGAAUUCAAGAAUAGCACAUUGUGGCAAGGAACAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI13		
		GGGAAUUCAACACCACUAUUGUUGGCAAGGAAACAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI149		
		GGGAAUUCAAGACACAACAUGGUGGCAAGGAACA-AUGGAGUGAUCUGAUACUACGAGCUCGAC	XI108		
		GGGAAUUCAAGUACGGCAAGGAGUACAUCGUAACAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI107		
		GGGAAUUCAACACCACUAUUGUUGGCAAGGAAGUAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI129		
	XIV32	GGGAAUUCAACACCACUAUUGUUGGCAGGGAAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC			
	XIV5	GGGAAUUCAAGUACGGCAAGGAGUACAUCGCAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC			
		GGGAAUUCAACACUACCUGGGUGGCAAGGAACCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI101		
		3′ GUUCCGUUCGAAAUAAC5′ **Poly-A Apical loop**			
		GGGAAUUCAACAACUACCAAUAGGACCCAGCCUA-AUGGAGUGAUCUGAUACUACGAGCUCGAC	XI30		TAR
		GGGAAUUCAACCACCUCCUAGUGACCCACUGCACUAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI70		TAR PBS
		GGGAAUUCAAUUACCUCCGGGACGCUCACCACCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI63		TAR SD
		GGGAAUUCAACAACACUUAUCGACUACCUGUCCCCAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI15		
	XIV25	GGGAAUUCAACACUACUCUACGGCUCGAAGCCCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC			
		GGGAAUUCAACAACACUACUGACACUGUA-CCCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI105		
		GGGAAUUCAAAACACCUCCUCCAGCCUCCCAGCA-AUGGAGUGAUCUGAUACUACGAGCUCGAC	XI142		TAR SD
		3′ UCGAGGGUCCGA5′ **TAR Apical loop**			
	XIV48	GGGAAUUCAAAACCACAACGGCUAACCACUGCCCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC			
		GGGAAUUCAAGGAGCACCACUUGGUCCACUGCCA-AUGGAGUGAUCUGAUACUACGAGCUCGAC	XI134		
		GGGAAUUCAAUCUGCUCCGCCGGUGCACCAGACCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI20		-
		GGGAAUUCAACACCACUAUUGUUGGCAAGGAAGUAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI129		
		GGGAAUUCAAUCUACUAGCCACGCCGACACCAACAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI103		
		GGGAAUUCAACAACACUUAUCGACUACCUGUCCCGAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI15		
		GGGAAUUCAACAACGACAUGGCUUCACUGACGCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI3		PBS
		3′ UGAGUGGUCA5′ **SD Apical loop**			
	XIV37	GGGAAUUCAACACUACCGACCGUCCACACCAGCCAAUGGAGUGAUCUGAUACUACGAGCUCGAC			
		GGGAAUUCAACACGAUAGGAACAACACAAGAAACAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI73	x 3	
		GGGAAUUCAACACGAUAGGAACAACACAAGAAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI65		
		GGGAAUUCAAACACUACUACGGAACUGCCUGAGCAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI117		
		GGGAAUUCAACUGACGCCCUCCUGCUGCAAGCCC-AUGGAGUGAUCUGAUACUACGAGCUCGAC	XI110		
		GGGAAUUCAACAACACCUGACCACAACUA-AGACAAUGGAGUGAUCUGAUACUACGAGCUCGAC	XI122		

RNA aptamers targeting the HIV-1 5’ UTR

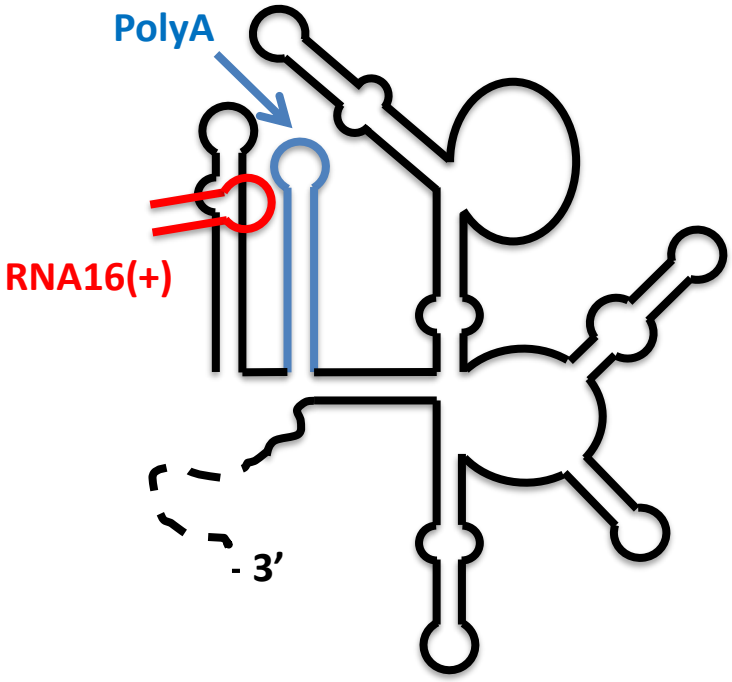


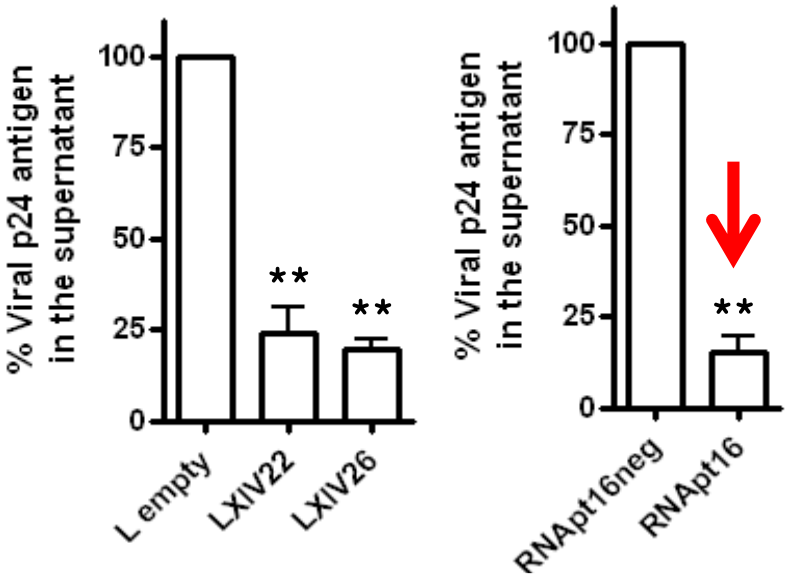


Structural analysis of isolated aptamers revealed a highly conserved 16 nt long consensus structural RNA domain.

RNA16(+) is an *in silico* designed minimal RNA aptamer consists in a 4 bp helical region closed by an 8 nt-long closing loop. Nucleotide sequence of the loop is complementary to the HIV-1 PolyA domain.

Anti HIV-1 5'UTR Aptamers

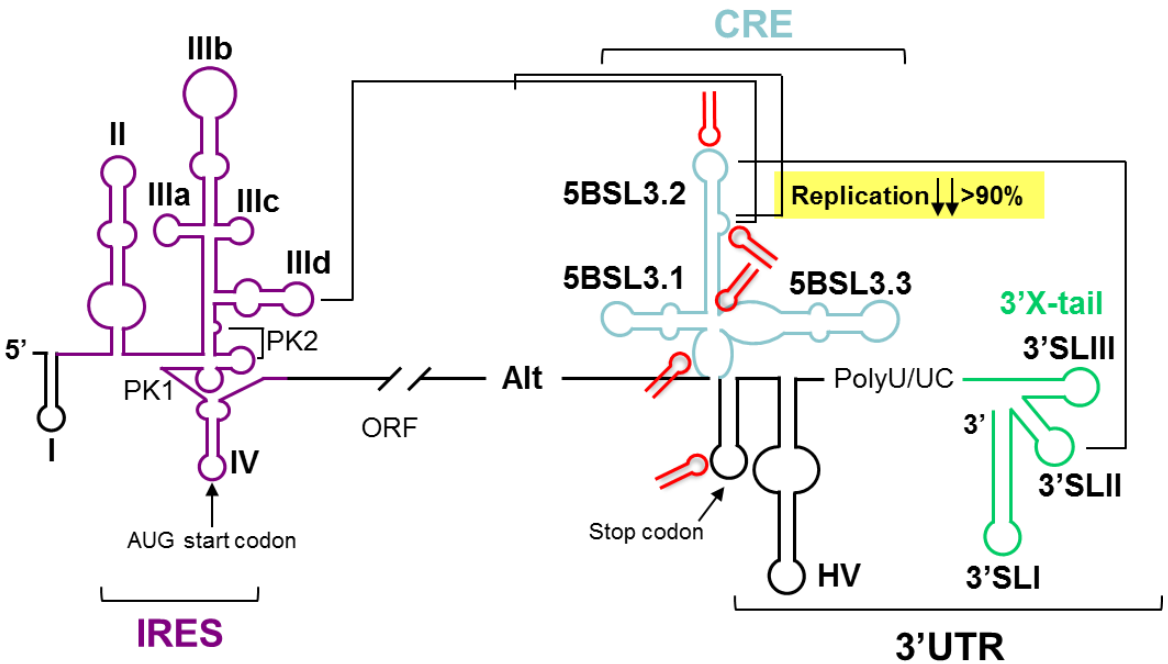




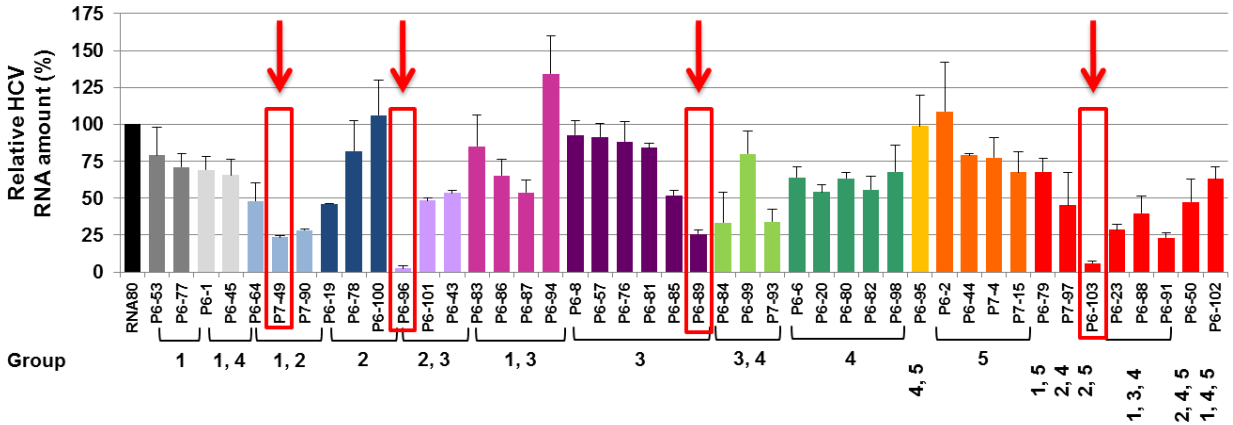
The RNA16(+) inhibits up to 85% HIV-1 viral particles production in a cell culture assay

The RNA16(+) is the smallest aptamer molecule ever described

Aptamers targeting the HCV CRE



Anti HCV CRE RNA aptamers inhibit the viral replication up to 90% in a cellular subgenomic replication system



Conclusions

- Aptamers offer a potential means for the development of efficient therapeutic drugs.
- Viral RNA genomes have been postulated as excellent candidates to be targeted by RNA aptamers.
- Viral RNA genomes contains highly conserved structural domains that are essential for the completion of the viral cycle. 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.
- RNA Aptamers targeting specific functional RNA domains are efficient antiviral agents.

Cristina Romero-López
Alba Fdez.-Sanlés
Soledad Marton
Beatriz Berzal-Herranz

F. J. Sánchez-Luque

Carlos Briones, CAB (CSIC/INTA)

CSIC Consejo Superior de Investigaciones Científicas ipbln

5th International Electronic Conference on Medicinal Chemistry
1-30 November 2019

sponsors: MDPI pharmaceuticals