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Press release

Structure Elucidation of a Kissing Complex and Application to the AIDS Virus

Scientists at the Jean-Pierre Ebel[1] Institute of Structural Biology in collaboration with teams at the European Institute of chemistry and biology[2] and Ottawa University have used innovating NMR[3] techniques to elucidate the specific recognition mechanisms between AIDS virus RNA[4] and a synthetic RNA. These results, published on July 8th in the review *Proceedings of the National Academy of Sciences of USA,* should provide a basis for the development of new therapies targeting viral RNA sequences.

Blocking HIV multiplication in patients is an important field of investigation in the fight against AIDS. One of the main goals of this research is to develop synthetic drugs capable of preventing viral replication after infection. For multiplication, the virus must duplicate its genetic material during a process called replication. During replication, several important cellular factors must bind to a regulatory RNA sequence of the HIV genome called TAR. One of the important AIDS research topics is therefore the development of synthetic RNAs capable of binding with a strong affinity to this regulatory sequence, thereby preventing viral replication.

Scientists at the European Chemistry And Biology Institute first isolated synthetic RNAs capable of specifically binding part of the loop-forming TAR sequence from a bank of more than 100 billion different oligonucleotides[5], (cf. figure : light blue and dark blue). These RNAs, which also form a loop (orange, red and yellow), bind to the TAR sequence by forming a complex structure called a *kissing complex* due to the pairing[6] of the two RNA loops. Surprisingly, the researchers found that synthetic RNAs which bind with the highest affinity to the TAR sequence all have a pair of GA bases that remain unpaired to those of the TAR part which form a loop.

To understand the role of this base pair and to permit synthesis of RNAs capable of binding more effectively to the viral regulator sequence, it was necessary to precisely elucidate how this binding takes place and define the essential parameters for its stabilization. By developing innovative NMR tools for the structural study of RNAs in solution, IBS and Ottawa University scientists determined with a very high precision the structure of the complex formed by the two RNAs in solution and unraveled the crucial role of the GA base pair. They found that the insertion of a GA pair allows the stabilization of the complex by the pairing of two additional base pairs. They also showed that the G A pair has a determinant role in stabilizing others *kissing complexes*.

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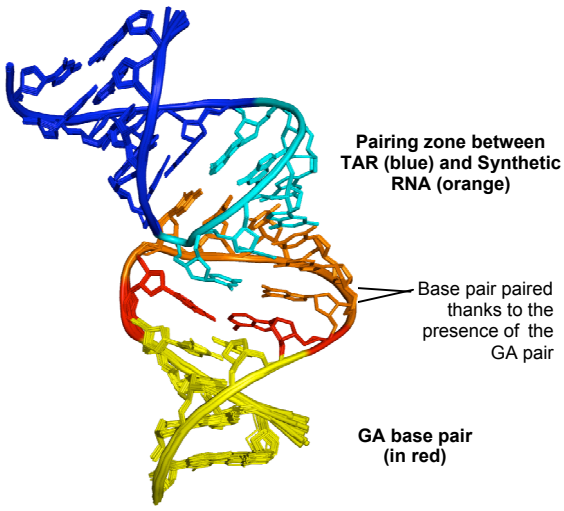
[3] NMR is the phenomenon by which a nucleus of an atom absorbs electromagnetic radiation at a specific frequency in the presence of a high magnetic field. It has applications in physics, chemistry and medical imaging.
[4] RNA carries the genetic blueprint of the virus, like DNA in man



Kissing complex between HIV TAR sequence (dark blue and light blue) and synthetic RNA (yellow, orange and red)

Thanks to this progress in our understanding of RNA/RNA interactions in *kissing complexes*, researchers will be able to pursue the research ofbetter targeted and more resistant synthetic RNAs, capable of blocking HIV replication. These results also open up new prospects for the design of biochemical tools to understand and control the biological functions in which loop-forming RNAs are involved.

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Reference of the article :

Van Melckebeke, V., Devany, M., Di Primo, C., Beaurain, F., Toulmé, J.J., Bryce, D. & Boisbouvier* J. *" Liquid Crystal NMR Structure of HIV TAR RNA Bound to its SELEX RNA Aptamer Reveals the Origins of the High Stability of the Complex ". Proc. Natl. Acad. Sci. USA*, 105, 9210-9215 (2008).

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