NMR spectroscopy constitutes, next to X-ray crystallography, one of the two primary methods for determining the three-dimensional structures of macro-biomolecules, that is, proteins and nucleic acids - DNA and RNA. The knowledge about the 3D structure of these molecules is crucial to understand the functioning of living organisms on the molecular level, but it also has a range of important practical applications. For example, the determination of the spatial structure of a viral RNA can be the first step towards the development of drugs interfering with replication of that pathogen.

In the case of NMR spectroscopy, three-dimensional structure determination is made possible through the measurement of distances between pairs of hydrogen atoms within the studied protein or nucleic acid molecule. Using hundreds or thousands of such distance measurements the 3D structure of the studied system is then reconstructed with specialized algorithms. One of the known limitations of this methodology is the fact that classic NMR experiments can only measure distances between pairs of atoms located relatively close in space to each other - up to around 5-6 Angstroms (Å; 1 Å = 10^{-10} m). When we realize that each distance measurement is subject to an experimental uncertainty and that these uncertainties add up, then we will understand that the further two atoms are located the less accurately their reciprocal distance is determined. In other words, classic NMR methods determine the local structure within a macromolecule very-well, but the global structure is subject to much larger overall uncertainty. This constitutes a serious limitation on the accuracy of NMR-determined structures and the scientists working in this field have long searched for additional types of experiments allowing to measure much longer distances by NMR.

It turns out that introducing a paramagnetic group - that in one bearing unpaired electrons - into the studied system can provide an opportunity to measure longer distances. Such paramagnetic moieties can be supplied by, for example, metal ions with not fully occupied d or f electronic sub-shells, such as lanthanide ions. The presence of such an ion in the molecule provides the opportunity to measure - through simple NMR experiments - distances as long as 30-35 Å, thanks to strong interactions between the unpaired electrons and the different atoms within the studied system. These interactions, also known as “paramagnetic effects”, have been successfully used in NMR spectroscopy of proteins for over two decades now, allowing to determine more accurate structures, as well as, helping with tackling such aspects as studying interactions between different proteins or between proteins and small-molecule drugs. On the other hand however, paramagnetic effects are not currently finding a wide use in NMR spectroscopy of nucleic acids. This is certainly not caused by their lack of appeal for NMR of nucleic acids - as they could constitute an even greater game changer for NMR studies of these systems - but rather by technical difficulties with introducing paramagnetic groups into this kind of molecules. The current project aims at resolving this issue by the development and characterization of short nucleic acid fragments capable of tightly interacting with lanthanide ions. Such molecules will be designed through identification and isolation of lanthanide binding sites located within much larger DNA systems, previously reported in the literature to tightly interact with lanthanide ions. Such “minimal” lanthanide binding DNA fragments will then be introduced (“implanted”) into a series of other systems, both DNA and RNA, to support their NMR structural and functional studies by inducing the paramagnetic effects. If the proposed research will prove to be successful, the obtained Lanthanide Binding Oligonucleotides (LBOs) will provide the scientists employing NMR spectroscopy with a general tool of introducing paramagnetic groups into nucleic acid systems.