In an exciting scientific breakthrough, we have discovered that nucleic acids (DNA and RNA) can activate an enzyme called peptidyl arginine deiminase 4 (PAD4) in a way that could transform our understanding of inflammatory diseases like rheumatoid arthritis (RA). This project aims to elucidate how this activation works.

PAD4 plays a crucial role in a process called NETosis, where white blood cells (neutrophils) release DNA to trap and kill bacteria. This process involves PAD4 modifying proteins in the cell's nucleus, leading to DNA release. While vital for fighting infections, excessive NETosis can contribute to chronic inflammatory diseases like RA. In RA, PAD4's activity is linked to the generation of molecules that the immune system mistakenly attacks, causing joint damage.

PAD4 needs high levels of calcium to work, much higher than what's typically found in cells. This raised the question: How does PAD4 get activated under normal conditions? Previous research showed that molecules similar to those found in the body, such as heparin, can activate PAD4 at lower calcium levels. This project will explore whether DNA and RNA can do the same.

Our team will investigate how different types and lengths of DNA and RNA affect PAD4's activity. Preliminary results are promising, indicating that longer and specific structures of DNA are particularly effective. We will use cutting-edge techniques to measure how strongly PAD4 binds to these nucleic acids and how this interaction changes PAD4’s structure and function.

To see how these findings apply in living cells, the team will use genetic engineering to create cell lines with PAD4 that either can or cannot bind DNA. These modified cells will help uncover the implications of PAD4 activation by DNA. For example, they will look at how these cells respond to inflammation and how their behavior changes when PAD4 cannot interact with DNA.

A particularly exciting part of the project involves developing short DNA sequences (aptamers) that can either boost or inhibit PAD4 activity. These aptamers could become the basis for new treatments, fine-tuning PAD4’s activity to fight diseases like RA without the side effects of current therapies.

By understanding how nucleic acids activate PAD4, the research could pave the way for new therapies for inflammatory diseases. It might also reveal new roles for PAD4 in gene regulation and other cellular processes, broadening our knowledge of cell biology and disease.

The project brings together a multidisciplinary team of experts in biochemistry, cell biology, and structural biology. They will use state-of-the-art equipment and techniques to unravel the complex interactions between PAD4 and nucleic acids, aiming to translate these findings into real-world medical advances.

This research holds the potential to revolutionize our approach to treating inflammatory diseases by targeting the fundamental mechanisms of PAD4 activation. It represents a significant step towards developing more effective and targeted therapies, improving the lives of those suffering from conditions like rheumatoid arthritis.