Bringing chemistry to life to treat rare diseases

Scientists in the Next Generation Chemistry theme at the Franklin are part of an international academic-industry consortium to accelerate the development of nucleic acid therapeutics.

Made up of DNA or RNA strands, therapeutic oligomeric nucleic acids can modify the expression of faulty genes that cause disease. Therapeutics based on these molecules have the potential to revolutionise the treatment of both rare and common diseases, including cancer, but challenges surrounding how they are manufactured and delivered into the body hamper development. We also often do not understand what drives their mechanism and hence their success.

As collaborators with the Medical Research Council's Nucleic Acid Therapy Accelerator (NATA), the Franklin team are finding new ways to deliver nucleic acids, in the form of these so-called oligonucleotides, into cells.

Targeting the genetic cause of disease

For rare conditions with low patient numbers, congenital diseases like heart defects and inherited degenerative diseases like Huntington's, are typically underserved by commercial drug developers. Rather than drug treatments, therapies for rare disease patients are limited to complex surgical procedures that correct defects or medications that can only treat the symptoms, rather than the cause, of a genetic condition. With advances in the genetic understanding of disease, the possibility of treating rare, inherited diseases is now within sight.

"There is strong interest in finding treatments for congenital or rare diseases where there's a clear understanding about the genetic defect that drives them. If we can directly correct the gene that causes that disease, then this might be an avenue for treatment," explains Professor Ben Davis, Science Director for Next Generation Chemistry at the Franklin.

Based across the Franklin and the University of Oxford, Professor Davis' group is contributing new knowledge to NATA's Delivery Challenge about how oligonucleotides are delivered and internalised within cells.

"Genetic diseases are caused by missing or faulty genes for the proteins needed for the body to function normally. By creating oligonucleotides made up of DNA or RNA for the correct version of the gene, and finding ways to get these into cells, we can give cells the recipe to create just enough of the protein needed to stop the progression of disease," adds Professor Davis.

Trailblazing a new class of medicines

Based alongside the Franklin on the Harwell Campus, NATA is a £30 million Medical Research Council Unit with a remit to work collaboratively with academia and industry to accelerate the development and manufacture of nucleic acid therapeutics ready for clinical trials within the next three to five years.

As well as funding researchers to solve the intracellular delivery and manufacturing challenges associated with nucleic acids, NATA is bringing together an international network of researchers, clinicians, businesses and charities to develop and drive impact from potential nucleic acid therapeutics. By establishing an international centre of excellence focused primarily on rare diseases, the Accelerator hopes to bridge the translational divide between nucleic acid research and clinical development in ways that would ordinarily be achieved by industry.

NATA Executive Director, Professor Nick Lench, explains: "Using genetically validated targets as a basis for therapeutics can be challenging. By working with partners like the Franklin, NATA has an ability to bring together chemists and biologists along with experimental facilities on the Harwell Campus to genuinely accelerate clinical development of this new class of medicines."

For any drug in development, chemists offer ways to modify a molecule to improve its delivery into a cell or reduce side effects.

"As well as working with the Franklin to understand and improve the stability of these molecules, or reduce their toxic side effects, our main challenge is to get the therapeutic to the right cell in the right tissue. Once it is there, it needs to traffic into the right part of the cell to perform its corrective function. Designing our oligonucleotides in this way very much sits in the sweet spot of what the Franklin can do," adds Professor Lench.

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>
> Professor Ben Davis

Looking through a molecular lens

For patients with incurable degenerative conditions, the hope is that if identified and treated early enough, nucleic acid therapeutics can fill an unmet need - a way to slow or stop the progression of disease in its tracks. Despite global enthusiasm, few nucleic acid therapeutics have reached clinical use, due in part to the mystery of how they are delivered into cells.

NATA is applying a molecular lens to this challenge, as well as working with rare disease charities and clinicians to understand which patients might be amenable to treatment and when.

For Franklin scientist Professor Davis, working on such bold problems is an exciting prospect.

"Our common theme at the Franklin is to do something very new by showing how the physical sciences can often uniquely unpick mechanism biology," says Professor Davis. "NATA is a wonderful project partner for us, because if we can shine an alternative light on how exogenous nucleic acids are delivered into and used by cells, there is no doubt that this will reveal new insights about their therapeutic power."