CML is a slow-progressing type of blood cancer that begins in the bone marrow and results in a high number of abnormal white cells (immune cells) in the blood. It is related to a structurally altered human chromosome called the Philadelphia chromosome. The Philadelphia chromosome creates a mutated gene: the BCR-ABL1 gene. In most cases, we don’t know what sets off this mutation, although CML has previously been linked to the effects of radiation. The mutated BCR-ABL1 gene produces an abnormal oncoprotein called BCR-ABL1 that acts as a tyrosine kinase, a molecule that causes continuous and uncontrolled faulty white cell production and eventually CML. This oncoprotein is the hallmark of the disease; more than 98% of patients with CML have it.

While treatment of CML has improved over the last 20 years, together with survival rates, conventional tyrosine kinase inhibitors (TKIs) used in therapy can have debilitating side effects. Now researchers are exploring a novel therapy for treating CML, which shows early promise of increased safety, fewer side effects, and increased efficacy. A team led by Dr Veronika Némethová and Dr Filip Rázga at Selecta Biotech, Slovakia, have developed a patented oligonucleotide therapeutics platform that has the potential to offer an even more precisely targeted therapy for CML.

This structure reduces the chances of the oligonucleotides binding to and working against the wrong mRNA molecules.

A very recent breakthrough

Until the beginning of the 21st century, the treatment options for CML were chemotherapy with very toxic cancer drugs, or bone marrow transplantation, a procedure that carries many risks. Over the past two decades, the development of TKIs has revolutionised the treatment of CML. TKIs are sophisticated medications that block the action of the abnormal BCR-ABL1 protein. Previously, the average survival time for CML patients was three to five years, but thanks to TKIs survival rates have improved dramatically with up to 89% of people with the disease surviving five years after their diagnosis.

Despite their sophistication, TKIs still have limitations. Up to 30% of patients either can’t tolerate or develop resistance to the medication, which eventually results in the development of a cancer that can evade treatment. TKIs can also have toxic side effects related to their non-specific action inside the body, such as weight loss, sickness, and skin rashes. There has also been an increase in the cancer’s resistance to treatment (TKI-resistant CML), and TKIs have a limited
The ESiNAR-X® platform offers accurate selective recognition and precise action against the defective BCR-ABL1 mRNA.

effect on CML stem cells, the primary cells from which all other disease cells are generated.

Oligonucleotide therapeutics promise new solutions

The need for more specialised treatments for diseases such as CML led to the even more recent development of new therapeutic ideas that enable control of the disease-causing genes by interacting with the mRNA. mRNA molecules are generated by genes and act as a template for producing the relevant proteins. These groundbreaking molecules are generated by genes and act as a template for producing the relevant proteins. These groundbreaking findings could spawn the next generation of treatment for CML.

Considering the challenges to developing treatments with no or very low treatment regimens which fail due to resistance or are limited because of drug intolerance. We have proposed multiple therapeutic oligonucleotides for different diagnoses which are at different stages of development. One of our therapeutic leads is currently under evaluation to get approval for clinical use. The BCR-ABL1 is in the final stages of preclinical development and will be proposed for authorisation soon.

What most excites you about a day working in the lab? We have been given the opportunity to make a difference in patient care and do what we do best, and so we feel responsible to contribute to the society and communities in which we operate. Our mission is to challenge alternatives to develop quality healthcare products through science-based evidence guides our professionals every day in everything we do. We continue to proactively look for solutions and challenge ourselves to make a difference in patient care through progressive therapeutic concepts that have the potential to redefine treatment outcomes.

Opening new treatment horizons

Challenges to developing treatments with no or very low side effects against CML, the researchers’ innovative technology is worth further investigation. As early results are promising, their findings could spawn the next generation of treatment for CML. The ESiNAR-X® platform offers accurate selective recognition and novel action against variant BCR-ABL1 mRNAs and could also block similar abnormal genes that cause other cancers and genetic diseases. This potentially means it could be a prototype for developing precision oligonucleotide combination treatments against numerous cancer and mutation-based conditions.

What inspired you to use the ESiNAR-X® platform for the treatment of CML? The strategies in CML therapy have mainly focused on improving the potency of TKIs and on overcoming the resistance driven by mutations in the BCR-ABL1 oncogene. Alternative approaches addressing current treatment challenges may be necessary for patients who fail to respond to TKIs and novel therapeutic modalities capable of targeting leukemic clones escaping TKI therapy could be game changers in the professional management of these patients.

The ESiNAR-X® platform could be a prototype for developing precision oligonucleotide combination treatments against numerous conditions.

What is the ESiNAR-X® platform for RNA-targeted therapy? Their research reveals that the mRNA-oligonucleotide combination treatments against numerous cancer and mutation-based conditions.

How does the ESiNAR-X® platform work? The smooth translation of oligonucleotide therapeutics into clinical use was hampered by fundamental shortcomings, the elimination of which required almost 20 years of intensive global scientific work. Enzymatic degradation and limited cellular internalisation, which represented an insurmountable barrier to clinical practice, have been relatively satisfactorily addressed by chemical derivatisation of oligonucleotides. However, their bioavailability and cellular uptake. On the other hand, regardless of the modifications, their promiscuity is far from being solved, even though almost 25 years have elapsed since the first drug was approved and despite more than 150 therapeutic oligonucleotides being involved in clinical trials today.

Our aim has always been to push the boundaries of what technology can produce, and we are proud to hold this unique proprietary technology that covers unconventional structural design of therapeutic oligonucleotides to significantly improve their characteristics in many ways. To highlight a few, unlike standard oligonucleotides the ESiNAR-X®-based therapeutics show: 1) exceptional specificity and do not interfere with native RNA off-targets; 2) spontaneous cellular uptake so less frequent and smaller doses can be used; 3) unprecedented safety as preclinical studies in rodents showed excellent tolerability; 4) exclusive selectivity in terms of triggering biologic effects only in target RNA-containing cells; 5) excellent efficacy in target RNA suppression evidenced by a reduction of target RNA levels to even 0% after a single application; 6) remarkable therapeutic efficacy being able to reduce leukemic cell burden in mice by 50% in just ten days; and 7) high versatility being fully adaptable to different RNA targets.

What further research is needed before your novel treatment becomes mainstream? The progressive success of the ESiNAR-X® platform is underlined by its theoretical applicability to any disease with a known genetic causality and/or unmet medical need. It can also be adapted to existing pipelines of oligonucleotide therapeutics in development. Rather than mainstream, we think about this technology as a vital and potent alternative to current treatment regimens which fail due to resistance or are limited because of drug intolerance. We have proposed multiple therapeutic oligonucleotides for different diagnoses which are at different stages of development. One of our therapeuticleads is currently under evaluation to get approval for clinical use. The BCR-ABL1 is in the final stages of preclinical development and will be proposed for authorisation soon.

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