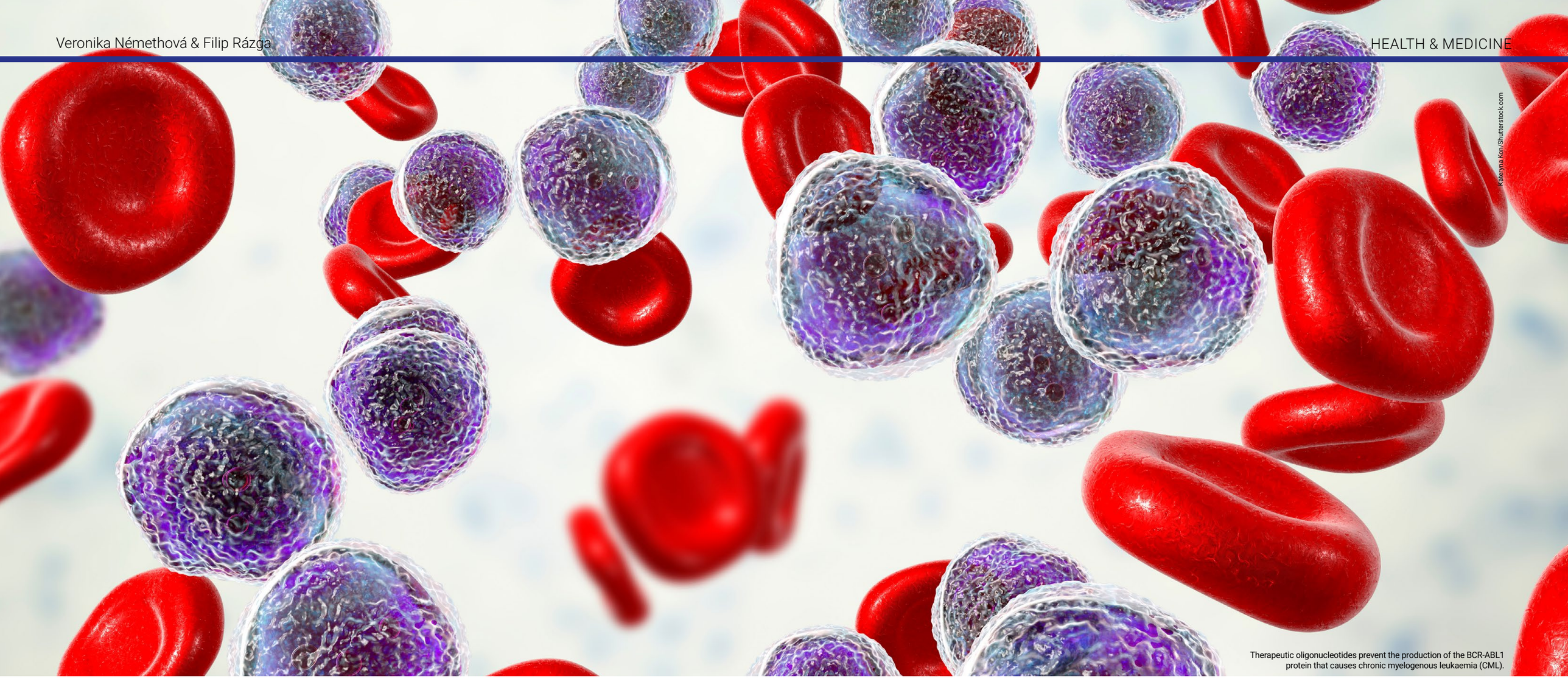


Kateryna Kon/Shutterstock.com

Therapeutic oligonucleotides prevent the production of the BCR-ABL1 protein that causes chronic myelogenous leukaemia (CML).

ESiNAR-X®

Precise action in the treatment of leukaemia

- Chronic myelogenous leukaemia (CML) is a blood cancer that starts in bone marrow.
- Treatments exist, but patients frequently have toxic side effects or are resistant to therapy.
- Dr Veronika Némethová and Dr Filip Rázga at Selecta Biotech, Slovakia, have developed a new way to treat CML using oligonucleotide therapeutics.
- Their novel approach means treatment is more targeted resulting in significantly fewer side effects.

Chronic myelogenous leukaemia (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.

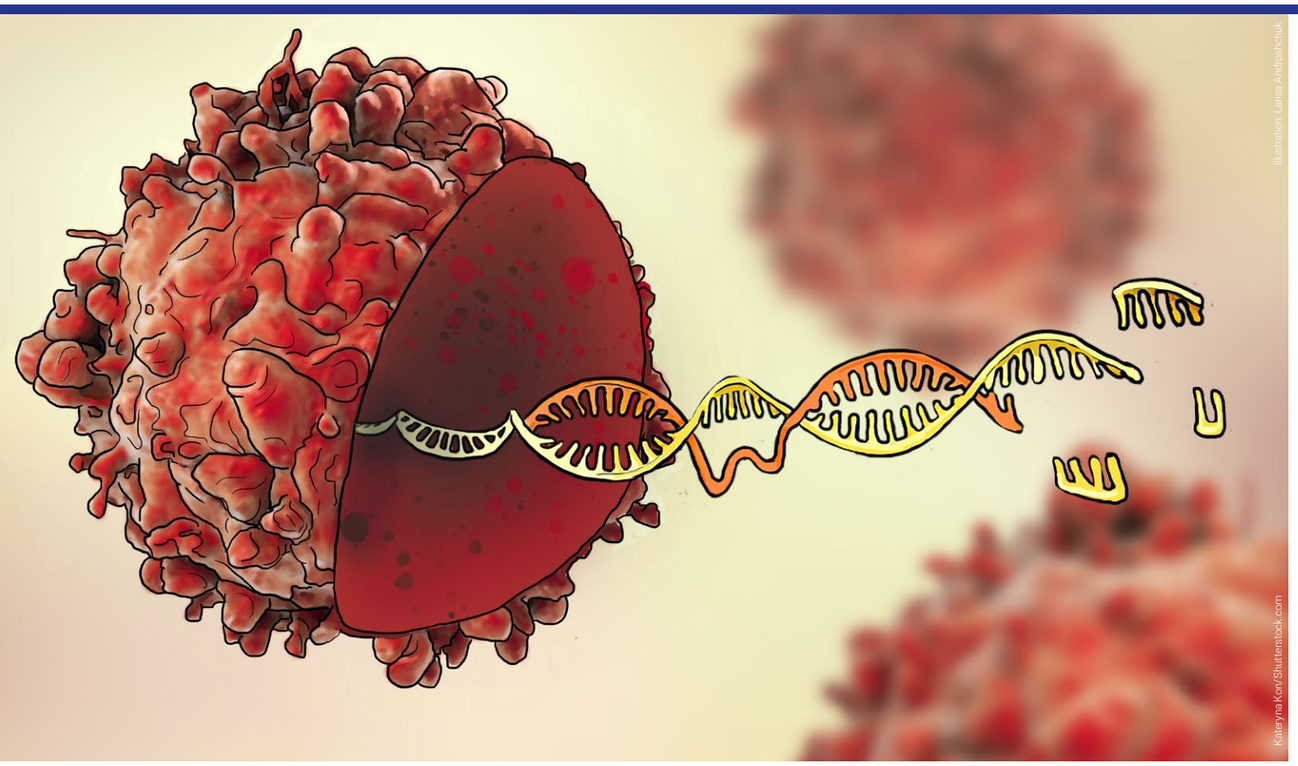
This structure reduces the chances of the oligonucleotides binding to and working against the wrong mRNA molecules.

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 Slovakian company Selecta Biotech, have developed a patented oligonucleotide therapeutics platform that has the potential to offer an even more precisely targeted therapy for CML.

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* mRNAs.

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 drugs are called therapeutic oligonucleotides. In the case of CML, these short chains of synthetic DNA work by specifically inducing the degradation of the *BCR-ABL1*-generated mRNA, thus preventing it from producing the disease-causing BCR-ABL1 protein. Oligonucleotides are superior to protein inhibitors in that they can stop a pathologic protein from even being produced.

To make these promising agents more target-specific and free of toxic side effects, Némethová, Rázga, and their team innovated a new treatment for CML, which uses a novel oligonucleotide therapeutics platform for RNA-targeted therapy. Their research reveals that this method is more precise and produces fewer side effects than conventional TKI medications.

How is the ESiNAR-X® platform different?

The team saw the potential of this new category of agents in treating CML but there were challenges to be overcome. Although more target-specific than TKIs, the oligonucleotide therapeutics nevertheless showed an affinity for non-target mRNA molecules, which meant this therapy still had significant toxic side effects.

The idea that led to the development of the team's proprietary platform ESiNAR-X® was to target one or two faulty mRNA sites to create a molecular structure that can attach and block both sites simultaneously. Since these mRNA sequences are not exactly next to each other but do, however, keep a specific distance between them, the team took advantage of this. They created a platform that consists of two mRNA sites-specific oligonucleotides that are connected by a linker of the relevant length. This structure reduces the chances of the two connected oligonucleotides binding to and working against the wrong mRNA molecules, preventing the disruption of the healthy mRNA functions and, therefore, the appearance of toxic side effects.

The structure specifically designed and developed by the team to target the *BCR-ABL1* mRNA and treat CML is called ASP210. ASP210 is currently at the final stages of testing before it can be tried in humans and so far has shown excellent results in animal studies for both safety and efficacy.

Opening new treatment horizons

Considering the challenges to developing treatments with no or very few 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.

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

Personal response

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 leukaemic clones escaping TKI therapy could be game changers in the professional management of these patients.

Oligonucleotide-based therapeutics represent the most powerful approach to block target RNAs. Authorisation of the first therapeutic oligonucleotide by the US FDA in 1998 sparked high hopes for the potential use of this new class of drugs for several human conditions. The success of the pilot drug rightly set off a wave of scientific and clinical enthusiasm, as it was a truly revolutionary tool for possible therapeutic intervention in diseases where a specific RNA plays a key, ideally causal, role in pathophysiology, such as *BCR-ABL1* in CML. The benefits resulting from the likely selective therapeutic effect in CML cells are so eminent that therapeutic oligonucleotides might be justifiably considered the most important future pharmacological perspective since the approval of TKIs for CML treatment.

How does the ESiNAR-X® platform approach outperform a singular-strand oligonucleotide equivalent?

The smooth translation of oligonucleotide therapeutics into clinic 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 to increase 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 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 progressiveness 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 therapeutic leads is currently under evaluation to get approval for clinical trials, ASP210 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 excel at what we do best, and so we feel responsible to contribute to the society and communities in which we operate. Our mission to challenge alternatives to develop quality healthcare products through science-based evidence guides our professionals every day in everything they 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.

Details

Veronika Némethová
e: nemethova@selectabiotech.com
t: +421 948 176 160

Filip Rázga
e: razga@selectabiotech.com
t: +421 948 176 160

w: www.selectabiotech.com
w: www.mediscine.eu
www.facebook.com/people/Selecta-Biotech-SE/100057121343368

Address
Selecta Biotech SE
Istrijská 6094/20
841 07 Bratislava
Slovakia

Funding
The Slovak Research and Development Agency, Contract No. APVV-15-0215 and APVV-19-0070
VEGA, Grant No. 1/0069/20
Non-profit civil association MediScine

Bio

Veronika Némethová is a professional in molecular biology and genetics. She is the coordinator of clinically oriented research as the Head of the Therapeutics Division at Selecta Biotech.

Filip Rázga is an expert in RNA structure and function with over 20 years of experience in RNA structure and oncology with a biotechnology focus. He is the CEO of Selecta Biotech and is responsible for its overall scientific management.

Collaborators

- Comenius University in Bratislava
- Biomedical Research Center of the Slovak Academy of Sciences
- National Cancer Institute in Bratislava
- University Hospital in Bratislava
- Institute of Hematology and Blood Transfusion in Prague

Further reading

Némethová, V, Rázga, F, (2018) Chronic myelogenous leukemia on target. *Cancer Medicine*, 7(7), 3406–3410.

Rázga, F, Némethová, V, (2017) Selective therapeutic intervention: a challenge against off-target effects. *Trends in Molecular Medicine*, 23(8), 671–674.

Khvorova, A, Watts, JK, (2017) The chemical evolution of oligonucleotide therapies of clinical utility. *Nature Biotechnology*, 35(3), 238–248

Hochhaus, A, et al, (2020) Expert opinion – management of chronic myeloid leukemia after resistance to second-generation tyrosine kinase inhibitors. *Leukemia*, 34, 1495–1502