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Complex science beautifully accessible



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A tailor-made antiviral therapy for SARS-CoV-2

- COVID-19 continues to impact the health of millions of people.
- Despite prophylactic measures, there is still no antiviral therapy specific for SARS-CoV-2 virus in patients.
- Scientists at Selecta Biotech have developed a potential new viral inhibitor that uses a novel technology.
- Their antiviral therapy reduced the amount of SARS-CoV-2 virus in patient cell samples by 98%.
- This novel technology stops the virus replicating by specifically binding to and inhibiting its RNA sequence.

The power of oligonucleotide therapeutics to tackle pathological proteins

DNA is the blueprint of life. Its long double strands comprise four nucleotide base pairs that, when arranged into long and complex sequences, form codes known as genes. Genes are converted into another type of

nucleotide strand called RNA, which serves as a template for the synthesis of proteins. Proteins are the molecular machines inside the cells of all living organisms – they influence what we look like, regulate biochemical reactions, and are vital for proper structure and function of the body. However, if an error occurs in the RNA, the

faulty instruction can lead to the creation of a pathological protein – one that can cause disease. While most therapies are designed to tackle these defective proteins, oligonucleotide inhibitors – short, single strands of synthetic DNA – go a step further by preventing these disease-causing proteins to be even produced in the first place.

Nearly three years after the outbreak of the COVID-19 pandemic, the SARS-CoV-2 virus is still causing lasting damage around the world, impacting the health and lives of millions. By September 2022, the World Health Organization reported more than 600 million cumulative cases as well as 6.5 million deaths associated with the disease. Preventive measures, such as widespread administration of vaccines, is playing a role in reducing the severity of cases. For those who require treatment, clinicians can try to treat the disease and its symptoms with existing drugs. However, an effective therapy specifically targeted against SARS-CoV-2 in patients is still lacking.

Specificity is key

Selecta Biotech have set their sights on tackling this challenge. The European company aims to develop and introduce into clinical practice a new generation antiviral agent targeted against SARS-CoV-2

viral RNA. This type of therapeutic is known as an ‘oligonucleotide inhibitor’. Oligonucleotides are short, single strands of synthetic DNA that target and bind to the corresponding base pairs of RNA, such as that from the SARS-CoV-2 virus. This binding inhibits the RNA from being translated into a protein, thereby preventing the protein’s function from being fulfilled.

To be effective, the design of the oligonucleotide inhibitor is vital. The oligonucleotide base pairs must be tailor-made to the sequence it

should block. In this way, the production of a pathological protein could be inhibited. Indeed, classical oligonucleotide inhibitors still run the risk of off-target effects which can cause side-effects or even toxicity within the patient.

To counter this, Selecta Biotech have developed a new technology named ESiNAR-X®, whereby RNA sequences are blocked by two oligonucleotides that are connected by a size-specific linker (Figure 1). ‘This improves the ability to recognise the correct target and dramatically reduces the chance that the inhibitor will inappropriately and inadvertently bind to other RNA,’ explains Dr Filip Rázga, CEO of Selecta Biotech.

When ASC1R was applied to cell samples taken from COVID-19 positive patients there was a 98% decrease in viral RNA.

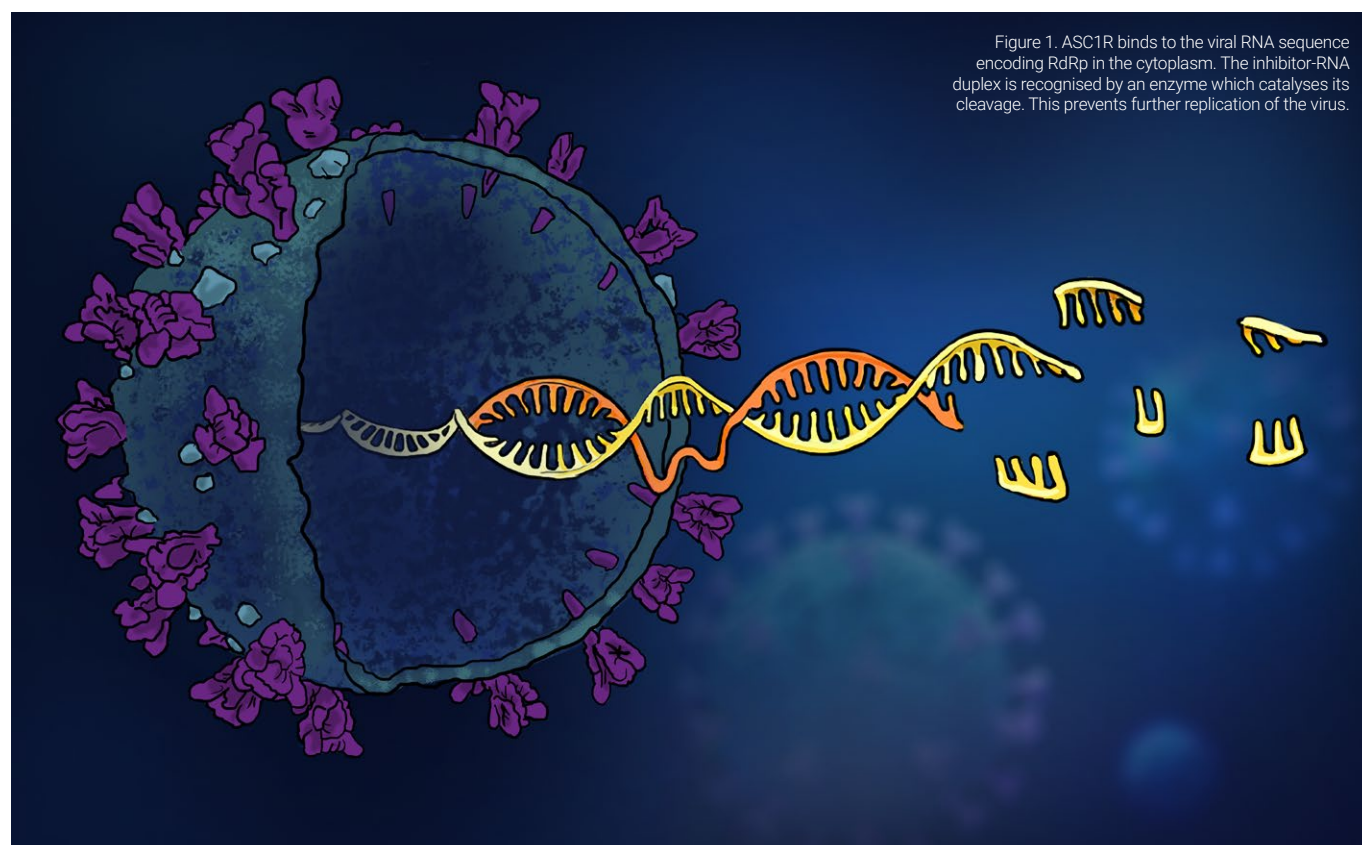
Inhibiting the viral lifecycle

In 2022, Selecta Biotech published the results of an investigation into the effectiveness of one such oligonucleotide inhibitor, known as

ASC1R. ASC1R specifically binds to two parts of the SARS-CoV-2 viral RNA that are localised at a defined distance from each other, which is key to this new technology. The RNA sequence that ASC1R blocks, codes for a subunit of the catalytic protein RdRp (RNA-dependent RNA polymerase) which has a vital role in the virus’s life cycle. RdRp speeds up the production of SARS-CoV-2 RNA from the RNA template. Without RdRp, the virus can’t replicate, stunting its takeover of the host’s cells.

In experimental studies, the effectiveness of ASC1R was clear-cut. Cultured cells transfected with SARS-CoV-2 showed a 94% reduction in





the amount of viral RNA they contained. Similarly, when ASC1R was applied to cell samples taken from COVID-19-positive patients there was a 98% decrease in viral RNA.

Aside from its clear-cut effect at reducing SARS-CoV-2 in cells, ASC1R has other benefits that increase its potential to be a successful clinical therapeutic. Perhaps most important is the therapy's safety. Studies on rodents showed that ASC1R has a favourable overall safety profile even at concentrations up to 50 times the effective dose.

The new technology can recognise the correct RNA target, reducing the risk of unwanted side effects or toxicity.

ASC1R also has an edge over other oligonucleotide therapies. 'One major challenge for oligonucleotide therapies is their ability to cross the cell membrane and enter the cell,' explains Dr Veronika Némethová, Head of Therapeutics Division. 'However, ASC1R spontaneously entered the cells without the need for another reagent to help it overcome this barrier.' Importantly, the antiviral agent doesn't continue to migrate into the cell nucleus where the cells' own DNA is located but remains in the cell cytoplasm where the viral RNA with which it binds is located.

Alternative applications

The concept of this new generation of oligonucleotide inhibitors isn't only limited to SARS-CoV-2. In fact, Selecta Biotech first investigated the therapeutic potential of the ESiNAR-X® technology in leukaemia treatment, and anticancer therapies remain their primary focus.

Many anticancer therapies fail to transition from the lab to the clinic because of side effects or toxicity in a patient. This is often due to a drug's promiscuity, meaning its inappropriate interactions with other



molecules or biological pathways. In the case of some anticancer drugs, side effects have even been accepted by clinicians and patients as a 'necessary evil'.

However, the company believes its new generation of oligonucleotide inhibitors could provide a much-needed solution. 'Our new technology, such as that exemplified by ASC1R, has an improved ability to recognise the correct RNA target and reduces the risk of unwanted side effects or toxicity,' explains Rázga. 'This new generation of oligonucleotide inhibitors has the potential to be a safer and more effective therapy against COVID-19 and other diseases alike.'

Personal response

The effects of ASC1R in cells and patient samples are conclusive. Were you expecting this and how did you feel when you first saw these results?

When proposing ASC1R, we built on our extensive experience with preclinical development of analogue inhibitors that showed remarkable effectivity in reducing the levels of their RNA targets encoding disease-causing proteins. When the pandemic struck in early 2020 it was not yet possible to estimate its devastating global impact, but information about the virus was published relatively soon. SARS-CoV-2 is a positive-sense unsegmented single-stranded RNA virus, meaning that the base sequence of the RNA corresponds to the later messenger RNA. It was then that we made the decision to implement our technology in the development of a tailor-made antiviral agent. At that time, we already had an optimised pipeline, so we were able to come up with the therapeutic lead candidate in as little as six months. All our inhibitors work by the same principle though ASC1R was the first one designed towards a viral disease. The effectivity of our inhibitor was evident already from the first tests performed on transfected cells. We soon realised that there was real potential in ASC1R that needed further investigation so we could ultimately help those who are dependent on medical care. The results on patient samples confirmed what we have seen with our other inhibitors, but we were more than happy with the results, mostly because at that time there was an urgent need for solutions that would help mitigate the impact of the pandemic. ASC1R appeared to be a tangible and promising solution with a possible global reach.

What are the planned next steps to help develop this oligonucleotide inhibitor into a clinical therapeutic?

Currently, we are intensively working to complete all preclinical data. Acute and sub-acute toxicology studies are currently ongoing in rodents and the preliminary results are very impressive. No ASC1R-associated toxicity was observed even at concentrations more than 50 times higher than the expected therapeutic dose. All our projects are milestone-driven, and we are currently focused on completing preclinical development to the point where there is sufficient scientific evidence to justify an application for clinical trial authorisation. Then the fate of the inhibitor will depend on the assessment of our data by the authorised institutions, which is why entering the clinic can be just a step away. However, we cannot rule out requests for additional results. We are ready for

both scenarios. Making this therapeutic solution available for patients who need it most is our core mission.

What is the potential for similar therapeutics to be developed against other diseases, aside from COVID-19 and cancer?

The development of new drugs requires two major steps: the identification of a therapeutically relevant target and the development of a compound capable of modulating its function. Increased understanding of the scientific underpinnings of the biological causes of many diseases has led to an upsurge in the number of potentially attractive molecular targets for therapy. Each of us carries unique genetic information, or DNA, which defines all the proteins in the body. Proteins do most of the work in our cells and are required for the structure, proper function, and regulation of the body's tissues and organs. To build a protein, a cell must make a copy of DNA, named RNA, which carries specific instructions for how to make that particular protein. If the instructions in the RNA are defective, a pathological protein is made and may cause a human disease. Traditional therapeutic approaches have been focused on inhibition of these defective proteins. Unlike conventional therapeutics, oligonucleotides have a distinguishing feature in that they can halt the process of producing a pathological protein before it even begins. They recognise and bind to RNAs, thereby either initiating their destruction or blocking them from further processing. By doing so, pathological proteins are not even built and cannot do damage in the body.

One of the unique features of the ESiNAR-X® platform is its versatility. The technology is universally applicable for any diagnosis with a known molecular causality, and our vision is to extend its use to other diseases as well. Currently, we have five inhibitors in various stages of development, including therapeutic leads for oncological, renal, and infectious diseases.

What inspired you to pursue this course of research?

We both worked in hospitals and saw the adverse – sometimes devastating – effects of some therapies on patients. That's when we decided to pursue clinically oriented research with the mission of developing quality healthcare products that have the potential to redefine treatment paradigms and improve, or even save, lives.

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Bio

Veronika Nemethova 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 Razga 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.

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Collaborators

Colleagues from the Biomedical Research Center of the Slovak Academy of Sciences and the National Cancer Institute in Bratislava

Further reading

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