INGENEIOUS

NEWS FROM COMBIGENE AB

ISSUE 2:2 • 2022

Welcome to special issue 2 of 3

Since the agreement with Spark Therapeutics, CombiGene has strengthened its positions in a number of areas, not least financially. The company is now actively looking for additional gene therapy assets for in-licensing and value-creating pre-clinical development.

In order to highlight our new position, we have decided to publish three issues of Ingeneious at a rapid pace to provide an in-depth picture of some of the areas that are important to us.

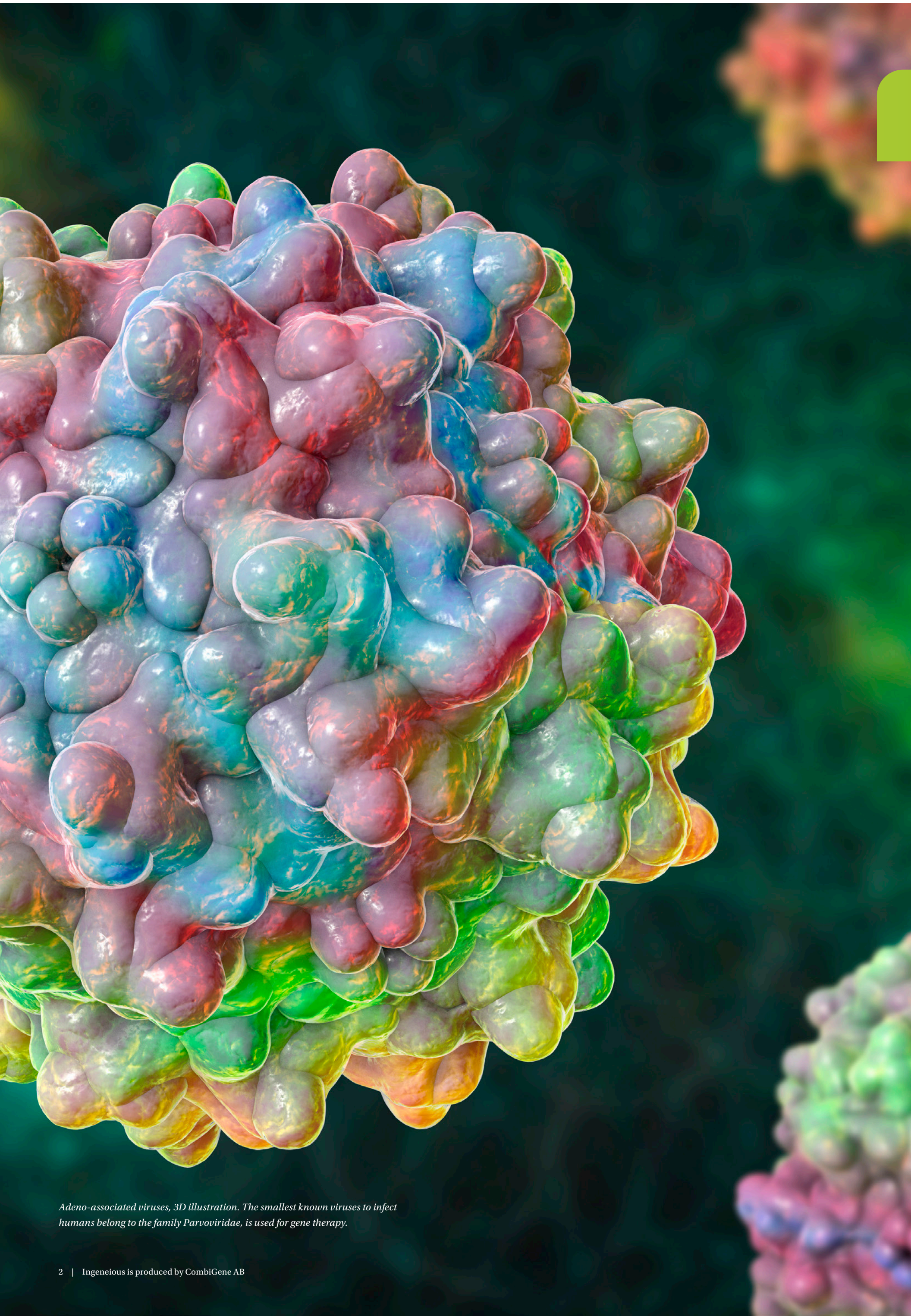
I hope you will find it a pleasant read.

Jan Nilsson,

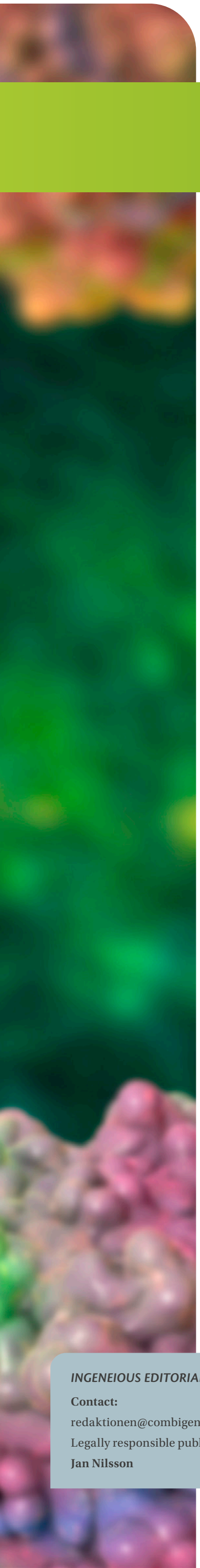
CEO

CombiGene

The gene therapy explorer



Adeno-associated viruses, 3D illustration. The smallest known viruses to infect humans belong to the family Parvoviridae, is used for gene therapy.



How gene therapy works

The goal of gene therapy is usually to treat genetic diseases, i.e., diseases caused by defective or missing genes, but also diseases where you want to increase the expression of functioning genes. Gene therapy is part of the Advanced Therapy Medicinal Products (ATMP) and uses DNA or RNA to regulate, repair, replace, add, or remove a gene. Since gene therapy is not carried out in gametes, the genetic modifications achieved through gene therapy are not hereditary.

There are different categories within gene therapy, but in this article, we will focus on the type of gene therapy in which a new gene is added to the patient using a viral vector.

Virus vectors as a carrier

It was when the researchers developed the technique of using viruses to insert new genes into the genome (all of an organism's genes) that the door to effective gene therapy was swung open. Previously, it had been possible to identify mutated genes and produce healthy genes in test tubes, but there was no technology to replace the mutated gene with a healthy one. With the revolutionary virus vector technology, development quickly took off.

The viruses used in gene therapy are "emptied" of their original contents. They thus consist of a shell that contains only the tools needed to enter cells and insert new genes and, of course, the healthy gene that will replace the mutated and disease-causing gene. Being emptied of its original content, the viral vector cannot spread or cause disease. The vectors that are used mainly come from AAV (adeno-associated viruses), retroviruses and adenoviruses.

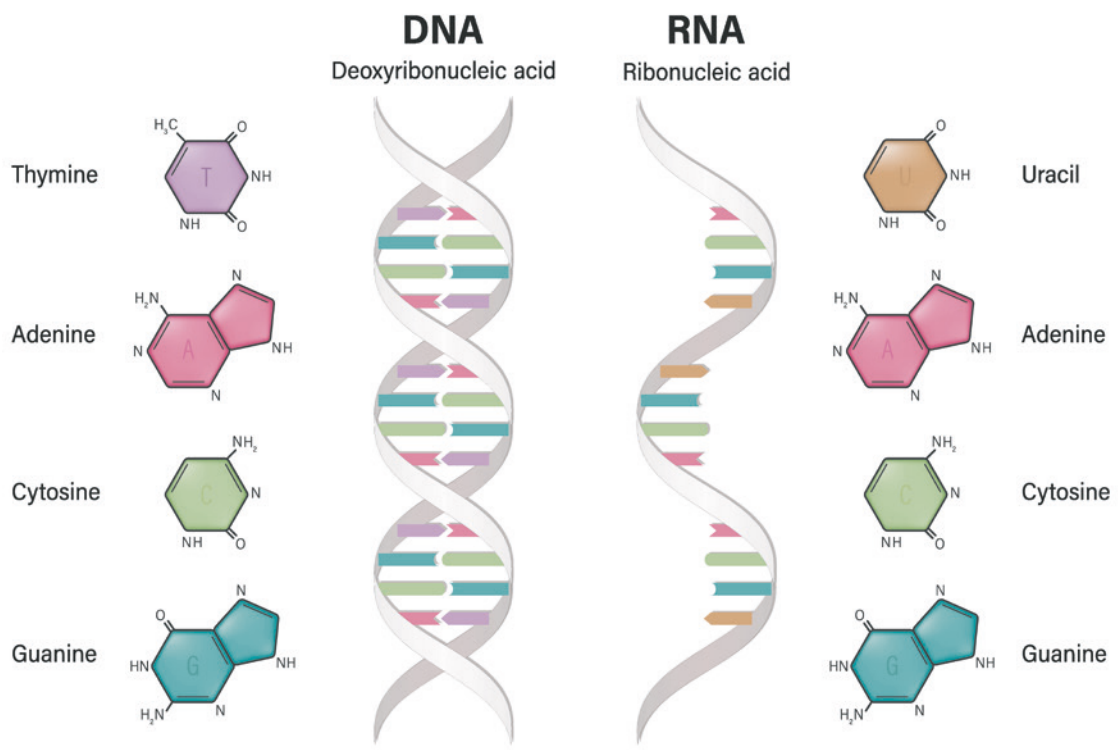
Vector-based gene therapy

Vector-based gene therapy can be likened to a transplant where instead of adding a functioning organ, a functioning gene is added. In short, a mutated and disease-causing gene is supplemented with a new and healthy gene. Cells can be extracted from patients through a blood test or a bone marrow sample. The sample is then modified with a new gene before being returned to the body. Alternatively, one can inject the new gene with its vector directly into the organ to be treated. When the gene begins to be expressed, the production of a functioning protein begins.

The goal is to cure

The ambition of gene therapy is to permanently cure diseases through one or possibly a few treatments. The difference from traditional treatment is thus significant. Many chronic diseases require continuous medication to relieve symptoms. Gene therapy has the potential to permanently cure with just one treatment.

Source: https://www.genteknik.se/genetik-och-genteknik/genmodifierade-organismer-gmo/mannis-ka-och-medicin/genterapi-2/sa-fungerar-genterapi/



INGENEIOUS EDITORIAL STAFF

Contact:
redaktionen@combigene.com
Legally responsible publisher:
Jan Nilsson

Production:
Form: **WibergComm from Scratch**
Text: **Columbi Communications AB**

CombiGene AB (publ)
Agavägen 52A,
SE-181 55 Lidingö, Sweden
info@combigene.com

CombiGene is listed on Nasdaq First North Growth Market.
www.combigene.com

THEME COMBIGENE

How to spell to success

One of CombiGene's success factors is spelled collaboration. The crown jewel of CombiGene's many collaborations is, of course, the collaboration and licensing agreement with Spark Therapeutics. In the autumn of 2021, Spark in-licensed the epilepsy project CG01, but the road to this success was paved by a series of successful partnerships.

CombiGene's collaborations can be divided into the following categories:

- **Research:** CombiGene does not have its own research capacity but aims to in-license interesting research assets from external researchers in academia and industry.
- **Business development:** CombiGene puts a lot of focus on identifying interesting gene projects to bring into the company. The company management works intensively with this but also collaborates with different types of partners.
- **Preclinical development:** This is one of the most important and value-creating areas for CombiGene and the company works with a number of partners in this field.
- **Clinical development and commercialization:** For gene therapy candidates developed for a large patient population, CombiGene's goal is to collaborate with leading international pharmaceutical companies. The prime example of this is the company's collaboration with Spark Therapeutics.
- **Industry collaborations:** CombiGene actively participates in several important industry associations.

CombiGene seeks collaboration on new projects

Over the past year, CombiGene has established the company as a player in the international pharmaceutical market. Strengthened by the collaboration and license agreement with Spark Therapeutics, CombiGene is now actively seeking additional gene therapy projects for in-licensing and value-creating development.

CombiGene is primarily looking for AAV-based projects since it is within this technology platform that the company has well-established knowledge in a number of key areas such as vector design (design of drug candidate), safety aspects and production. The disease areas that are in focus are correspondingly those where CombiGene has built up a solid knowledge, i.e., diseases of the central nervous system and metabolic diseases.

Having said this, CombiGene will at the same time have an open attitude towards possible projects and evaluate each opportunity on its own merits. CombiGene regularly participates in important partnering conferences, while the company conducts continuous dialogues with interesting actors in both academia and industry to identify interesting projects.

In the next issue of Ingeneious, we will take a closer look at how CombiGene has strengthened its organization to meet the future.

Living with epilepsy

Epilepsy is a disease that affects all aspects of life through its unpredictability. It is not possible to know in advance when a seizure will occur, which can lead to a constant worry for both patients and relatives. Epilepsy can thus limit life in a number of areas professionally, practically, and emotionally. It can be difficult to get a driver's license. You can refrain from holding your child in your arms because of fear of a sudden seizure. You can be limited in your career choices.

Epilepsy also affects the whole family, whether it is an adult or a child who has the disease. The need for priorities and choice of activities becomes even more important than in other families. Epilepsy can also affect how you perceive your own body. Desire and interest in sex can decrease or disappear and you may be worried about having a seizure when you have sex, even if it is unusual.

Epilepsy is also associated with feelings of guilt. You may feel that you cause problems for your surroundings by not being healthy. Relatives may feel guilty about not being able to put things right.

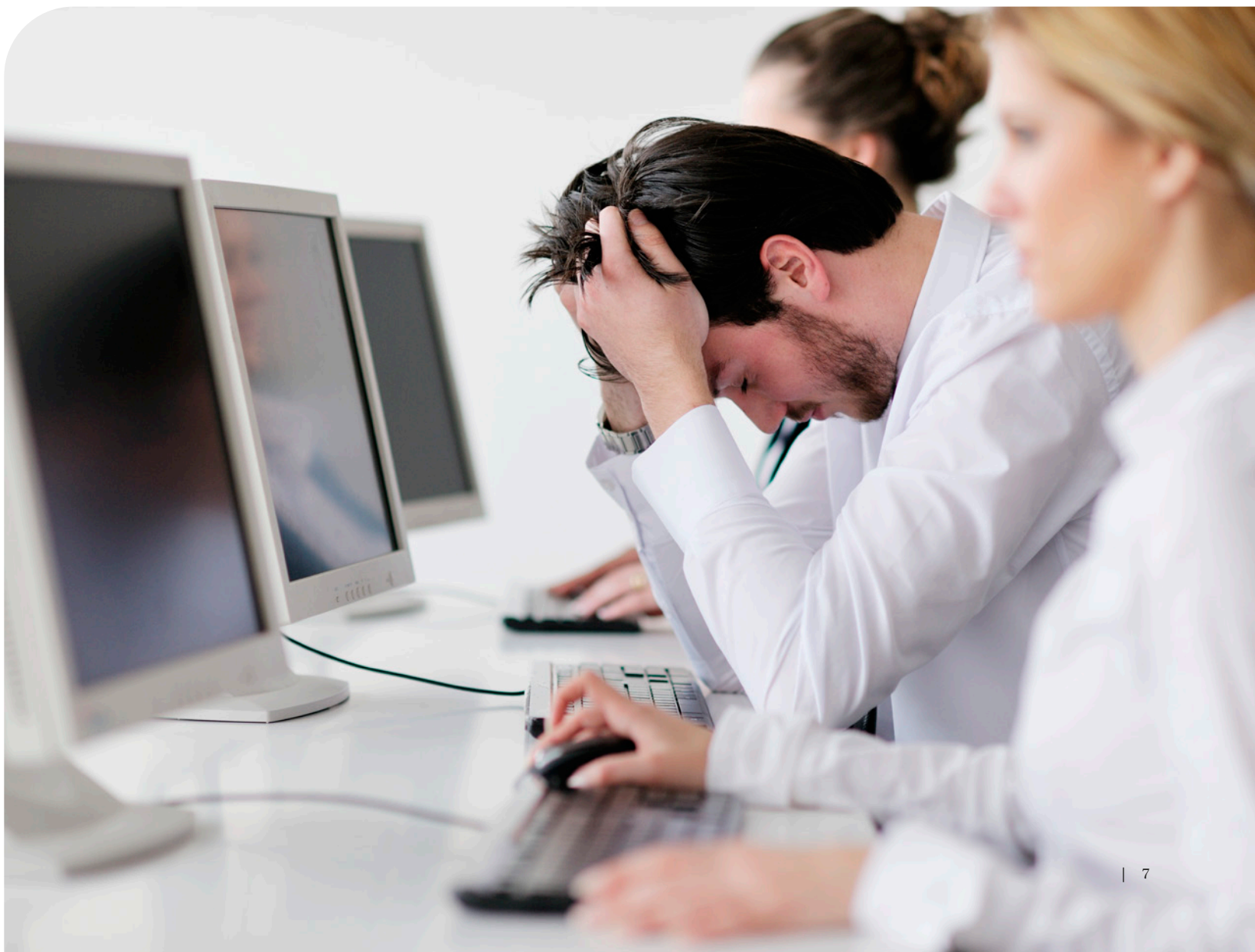
Epilepsy also often places demands on adaptations in the workplace. Depending on the type of work you have, the workplace may need to be adapted ergonomically. Sound, light, how to sit or stand and the possibility of breaks are all important components in creating a functional workplace.

The disease can to some extent be affected by one's way of life. Many people feel that the seizures occur more easily in certain situations, which situations are very individual. However, sleep deprivation is something that many people are sensitive to. Some may be sensitive to stress, others may not. The common perception that flashing lights induce epilepsy attacks is true only for a small portion of everyone with epilepsy.

If you have epilepsy, it is important that you do not avoid doing what you think is fun unless there are real factual reasons to abstain. With epilepsy, there is always a risk of unjustified restriction and isolation.

In the next issue of Ingeneious, you can read what Liz Ramsburg, Ph.D., and head of CNS research at Spark Therapeutics says about the collaboration with CombiGene.

Source: https://neuro.se/diagnoser/epilepsi/att-leva-med-epilepsi/



THEME LIPODYSTROPHY PROJECT CGT2

CGT2 has the potential to be classified as an orphan drug

Orphan drugs are a category of drugs developed for the treatment of very rare diseases. To be classified as an orphan drug in the EU, the disease that the drug is developed to treat may only occur in a maximum of five out of 10,000 people.

Developing treatment options for rare diseases is seen as urgent. Medicinal products classified as orphan medicinal products therefore enjoy specific advantages under Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan medicinal products. Similar legislation exists in the United States.

Partial lipodystrophy belongs to the group of rare diseases. Calculations show that there are about 2,000 patients in the United States and Europe. CombiGene believes that there is a good prospect of obtaining orphan drug classification once the project's final drug candidate has undergone the important proof-of-concept study.

When a drug candidate receives an orphan drug designation, it is provided with several significant benefits in the form of regulatory assistance, tax breaks, government grants, reduced fees, and long market exclusivity. Given the benefits of an orphan drug designation, CombiGene could potentially develop the lipodystrophy project CGT2 all the way to market in-house.

In the next issue of Ingeneious, you can read about CombiGene's important collaboration with Professor Ormond MacDougald at the University of Michigan Medical School.

Source: https://www.tlv.se/lakemedel/om-lakemedel.html

Interview with Per Lundin on CombiGene's Board of Directors

Tell us a little about yourself and your background and when you were elected as a member of CombiGene's board!

I have a broad background from the biotech industry. During the past 10-15 years, I have founded, led and been a board member of companies that mainly develop advanced therapies, from gene therapy and cell therapy to exosome-based drugs. I live in Oxford, England, where I work as Chief Business Officer at Evox Therapeutics Ltd, a company with about 150 employees that I co-founded in 2016 and which has since raised about SEK 1.5 billion in venture capital.

My expertise and experience are mainly within strategy and funding, commercialization of research assets, and, as a former patent consultant I also contribute within IP, which is always a critical component for creating value within biotech. I was elected to CombiGene's board in 2020 and have since seen how the team has developed the company into a name on the international biotech map, which is extra exciting for me who spends a lot of time with investors and pharmaceutical companies in both the UK and the US.

What are the key milestones in the company's development as you see it?

Looking in the rearview mirror, the cooperation and licensing agreement with Spark is of course an important milestone, but in many ways the agreements like this is solely achieved by disciplined work to create value over time, so several of the steps during the development of CG01 have also been significant, though less visible. Successful preclinical studies, scale-up and manufacturing, as well as strong patents are components that together drive companies such as CombiGene forward.

Looking ahead, business development will play a key role in the company and the ongoing efforts to expand the project portfolio will hopefully result in further projects being acquired or in-licensed, which will be an important milestone for CombiGene. The development of CG01 continues at full force, and the company has activities to look forward to in the coming years.

What does the agreement with Spark mean for CombiGene as a company?

Licensing agreements are in all respects a good mechanism for creating risk-adjusted value and the agreement with Spark has some specific characteristics that make it to a fantastic opportunity for CombiGene. Of course, the Spark collaboration contributes to positive cash flow and the fact that all research and development are paid by Spark is important for CombiGene and its shareholders, but in my opinion, it is even more important that the company in Spark has found a fantastic partner with the ambition and expertise to accelerate the project into the clinic development and hopefully to a global market. The agreement has also resulted in CombiGene making a name for itself within the global biotech arena in a completely new way, something that in turn will enable value creation by opening doors for future out- and in-licensing deals.

How do you think CombiGene will develop over the next three to five years?

I see a CombiGene that will move from being a preclinical company with a fairly small project portfolio to a company that runs a number of gene therapy projects in both preclinical and clinical phase, either inhouse or through out-licensing to global biotech or pharmaceutical companies. The biotech market has had a very rough time since mid 2021, which for a company like CombiGene – with the deal with Spark – can lead to new opportunities for business development and thereby value creation for the company and its shareholders.

About CombiGene

● *CombiGene's vision is to provide patients affected by severe life-altering diseases with the prospect of a better life through novel gene therapies. CombiGene's business concept is to develop effective gene therapies for severe life-altering diseases where adequate treatment is currently lacking. Development assets are sourced from an external research network and developed to achieve clinical proof of concept. Drug candidates for common diseases will be co-developed and commercialized through strategic partnerships, while the company may manage this process on its own for drugs targeting niched patient populations. The Company has an exclusive collaboration and licensing agreement for the CG01 project with Spark Therapeutics.*

The company is public and listed on the Swedish marketplace Nasdaq First North Growth Market and the company's Certified Advisor is FNCA Sweden AB, +46 (0)852 80 03 99 info@fnca.se.

CombiGene

The gene therapy explorer

CombiGene's vision is to provide patients affected bysevere life-altering diseases with the prospect of a better life through novel gene therapies.

www.combigene.com