INGENEIOUS

NEWS FROM COMBIGENE AB

ISSUE 3 • 2022

High activity in the industry – and at CombiGene

Welcome to a new issue of Ingeneious!

CombiGene is currently in a very exciting position in the company's development. Following the successful outlicensing of our epilepsy project CG01 to Spark Therapeutics in the autumn of 2021, we have intensified our efforts to find new projects for in-licensing while preparing the company to handle a growing project portfolio. You can read more about this in the extensive interview with Karin Agerman, CombiGene's Chief Scientific Officer. In this issue of Ingeneious there are also interviews with our new Chief Operating Officer Peter Ekolind and our new Senior Director In-licensing Birgitta Ståhl, both of whom are important in the leap that CombiGene is now preparing for.

The field of gene therapy itself also continues to develop at a rapid pace. During the first half of 2022, 372 clinical studies were conducted in a number of different disease areas (ARM, H1 2022). It is particularly gratifying to note that gene therapy is also making itself increasingly relevant in everyday clinical practice. More about this can be found in the article "Gene therapy holds its promise".

Jan Nilsson
CEO

CombiGene
The gene therapy explorer

THEME GENE THERAPY

Gene therapy ho

The level of activity in the field of gene therapy is high. During the first half of 2022, there were 372 clinical studies with different gene therapy candidates. Oncology is the dominant field, accounting for about 52 percent of all studies. In second place are diseases of the central nervous system, which account for 8 percent of the total number of studies followed by infectious diseases, hematology and genetic diseases, which together make up 16 percent of the number of studies. (ARM, H1 2022) The prospects that in the coming years we will see additional therapies that receive market approval are thus good.

Our partner Spark Therapeutics has developed the gene therapy which is used at Sahlgrenska University Hospital

Gene therapy is not just a field of research and development. There are already a number of approved therapies in clinical use. In Sweden, Sahlgrenska University Hospital in Gothenburg is the first hospital in the country to use a gene therapy for hereditary blindness. The patient is a woman with severe visual impairment on both eyes. Sahlgrenska also has plans to treat a child within short. (Lakartidningen.se 2022-09-16)

The gene therapy that Sahlgrenska uses is provided in Sweden by Novartis.

Treatment of spinal muscle atrophy in Sweden

The most severe variant of spinal muscle atrophy (SMA) is called SMA1 and affects young children up to 18 months of age. SMA1 is a rare hereditary disease in which the muscles atrophy. The children stop crawling and the lungs are affected and without treatment, SMA1 can be fatal. Research has progressed rapidly and in recent years there have been drugs available for daily medication. Further progress has now been made.

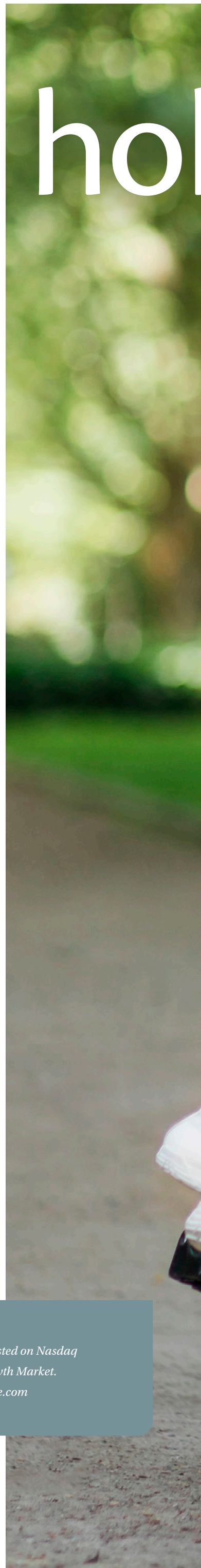
Earlier this year, a one-time gene therapy treatment was given to treat children with SMA1. The research shows that if a one-time gene therapy treatment is carried out before the child weighs 13.5 kilos, the motor neuron can continue to develop. The hope is that the children will be cured. (Swedish Radio, Vetenskapsradion Hälsa 2022-10-14)

Link to Läkartidningen (Swedish only)

https://lakartidningen.se/aktuellt/nyheter/2022/09/sahlgrenska-forst-i-landet-med-genterapi-mot-arftlig-blindhet/#:~:text=Nu%20har%20alltså%20en%20första,dubbla%20mutationer%20i%20genen%20RPE65.

Link to Swedish Radio (Swedish only)

https://sverigesradio.se/avsnitt/barn-far-inte-vaga-over-13-5-kilo-for-att-fa-genterapin-som-kan-bota-dem



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

lds its promise

The woman in the picture is affected by spinal muscular atrophy (SMA).
The image has been approved for publication.

CombiGene gears up

”The work of bringing in new projects naturally begins with finding interesting gene therapy assets that fit into our vision for CombiGene.”

When CombiGene outlicensed the epilepsy project CG01 to Spark Therapeutics in the autumn of 2021, it not only meant that the company received USD 8.5 million in upfront payment and the opportunity to receive an additional USD 320 million in future milestone payments. The agreement also meant that CombiGene in one stroke established itself as an important player in the international gene therapy market. Large pharmaceutical companies now follow CombiGene's operations with interest for future potential license deals and smaller players in industry and academia view CombiGene as an attractive partner for further development of their gene therapy assets. Ingeneious contacted CombiGene's Chief Scientific Officer Karin Agerman to talk about CombiGene business development and the efforts to identify new projects for in-licensing.

CombiGene is very active in its business development. Can you give an overall picture of this work?

“Gladly. Let me start by describing our business model. CombiGene does not itself research new gene therapy assets. We leave this to others. The first part in our business model is therefore to bring gene therapy assets from external researchers in academia or industry into the company. This is what we did with the epilepsy project CG01, which originated from professor Merab Kokaia's and associate professor David Woldbye's research at the universities of Lund and Copenhagen, and this is what we did with the lipodystrophy project CGT2, which we inlicensed from the Swedish company Lipigon.”

“The second part of the business model is to develop the gene therapy assets that we have inlicensed into preclinical or clinical proof-of-concept. Once we get this far, we have two options. For gene therapies aimed at large patient populations, we have the ambition to outlicense our gene therapy to a large pharmaceutical company with the expertise and resources to take the project through continued preclinical / clinical development and commercialization, just as we did with the CG01 project. When it comes to therapies that are being developed for the treatment of a limited number of patients, we are also open to taking a drug candidate all the way to market in-house.”

“This was a long background,” says Karin with a light laugh, “but I think it's important to understand how we work. Now to your question! CombiGene's business development naturally reflects our business model and primarily aims at two things: to find new and interesting projects for in-licensing on the one hand and out-licensing of projects that have reached proof-of-concept on the other. Where the emphasis lies varies over time. For several years, we worked intensively to find a partner for the epilepsy project CG01. Since Spark inlicensed this project, the emphasis has now shifted to bringing in new projects. So far in in the history of CombiGene, we have inlicensed two projects and outlicensed one. We have not yet faced a situation where we have the opportunity to take a project all the way to market on our own.”

Let's take a closer look at your efforts to find new projects. How does this work in concrete terms?

“There will be a long answer to this question too I'm afraid because it's a very extensive work that includes several components. Let me start by saying that CombiGene is continuously working on this part of our business development, and lately we have intensified our efforts, not least after the agreement with Spark. The work of bringing in new projects naturally begins with finding interesting gene therapy assets that fit into our vision for CombiGene. This work is ongoing in several different ways.”

“With the help of students from Karolinska Institutet, we have mapped academic groups working with different forms of gene therapy and we continuously follow their work. Similarly, with the help of patent lawyers, we have mapped gene therapy-related patents in the Nordic and Baltic countries, which means that we have a good overview of the work being conducted in industry/academia in Sweden and other Nordic/Baltic countries. Of course, we at CombiGene are also active in finding new interesting projects at conferences and within our personal networks – most of us who work at CombiGene are researchers at heart. CombiGene's board of directors, which also includes trained scientists, also participates actively in the work of finding new projects.”

INTERVIEW WITH KARIN AGERMAN, CHIEF SCIENTIFIC OFFICER

”We have a wide field of vision when evaluating potential projects. The creativity in the research world is absolutely astounding!”

”In addition to this, we have commissioned a consulting company to scout interesting gene therapy assets globally so that we do not limit ourselves to what is available in the Nordic region. Finally, with the help of a postdoc from Karolinska Institutet, we have also mapped out the interesting opportunities that exist among orphan drug candidates in the U.S. To summarize, we work broadly with many different activities.”

It sounds like an impressive piece of work, but what are the concrete results of your efforts?

“So far, we’ve looked at several candidates. They have not fit into CombiGene’s operations for various reasons, reasons which include the lack of a patent or the lack of possibilities to apply for patents, the fact that patients cannot be diagnosed in a good way and that there are no good animal models. There have also been pure business reasons that have made us decide not to move forward.”

“In addition to this, we have a fairly significant list of projects that we are now actively looking at. It is of course crucial for CombiGene to find new, interesting projects for in-licensing. At the same time, it is at least as important that we turn down projects that for one reason or another do not suit our business. Apple founder Steve Jobs said he was just as proud of the products Apple chose not to develop as the products they actually launched. CombiGene has the same attitude.”

Is there a project where you are close to signing an agreement?

“As a listed company, CombiGene cannot answer questions like this. When there is an agreement in place, we will of course announce this immediately, but before that we will not make any comments. What I can say is that negotiations of this kind are complex since an agreement on gene therapy assets must cover a variety of details. Reaching a final agreement is therefore a process that takes a long time even in the best of worlds.”

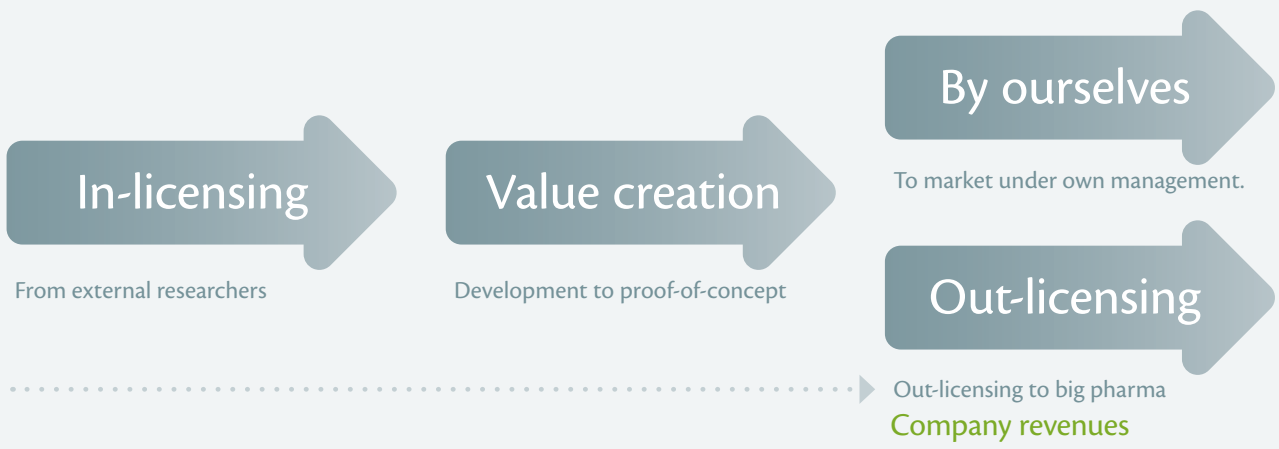
I understand. If we take a slightly different perspective, what is the overall goal for CombiGene right now?

Our ambition is to build a broad project portfolio that includes projects in several phases of drug development, ranging from projects in really early phase to projects in clinical development and thus contribute to gene therapies being commercialized and put to clinical use.”

“One important reason to build a broad portfolio and continuously replenish it with new candidates is that far from all drug candidates make it all the way to market approval. On the contrary, the majority of all the world’s pharmaceutical projects fall short somewhere during preclinical or clinical development. There can be many reasons for this. The drug candidate may not have the intended therapeutic effect or may have a non-acceptable safety profile. During the development work, alternative therapies from other companies may also emerge that turn out to be more attractive than what you yourself are doing.”

“CombiGene’s ambition to build a broad portfolio thus aims, among other things, to reduce the risk in the company by not putting all the eggs in one basket. One should not be surprised if a project does not make it through the entire preclinical and clinical development. On the contrary, it is unfortunately something to be expected. The important thing is to find out as early as possible that a project does not have the prerequisites to become an approved therapy. The sooner this is discovered, the less resources have been put into the project. Good economy, quite simply.”

Our business model - the principles



”Our ambition is to build a broad project portfolio that includes projects in several phases of drug development.”

INTERVIEW WITH KARIN AGERMAN, CHIEF SCIENTIFIC OFFICER

Are there any specific disease areas or indications CombiGene is looking for?

"Yes and no. We have said that we are first and foremost looking for AAV-based projects because it is this type of vectors that we have extensive experience with. We have also said that we are happy to take in projects in the areas where we are active in today, i.e., diseases related to the central nervous system and metabolic diseases."

"But we've also said that we in no way have locked ourselves to a specific vector technology or a specific disease area. Gene therapy offers so many opportunities and there are a number of disease areas and health conditions that are potentially interesting for us and we have a wide field of vision when evaluating potential projects. The creativity in the research world is absolutely astounding!"

If we turn the question around a bit. Are you primarily interested in diseases that affect many people or can you also see yourself developing therapies for very severe diseases that only affect relatively few people?

"I think you can see the answer already in our current project portfolio. The CG01 project is aimed at people with epilepsy, a disease that affects a large number of people and where the potential market for a new treatment is very large, not least in the context of gene therapy. The CGT2 project, on the other hand, is being developed for the few people affected by partial lipodystrophy. In other words, we are open to working with both large and small indications. It goes without saying that therapies targeting diseases that affect many people have substantial commercial potential, but also therapies developed for the treatment of rare diseases can be commercially interesting."

"In both the EU and the U.S., there is something called orphan drugs. This refers to drugs that are being developed precisely for the treatment of rare diseases. Developing therapies for these diseases does not have the same innate commercial potential as therapies that target common diseases and health conditions. In order to encourage the pharmaceutical industry to nevertheless develop therapies for these diseases, the authorities have developed regulations that aim to stimulate this particular type of development, so-called orphan drugs. During the development of a treatment for rare diseases, you can apply for so-called orphan drug designation, which entails, among other things, major cost advantages during the development process. If you are successful in your development and obtain market-approval for your treatment, you can obtain so-called orphan drug status with various advantages in terms of price and market exclusivity. From CombiGene's perspective, therapies that are developed for both large and small indications are thus of interest also from a strictly commercial perspective."

Then I have only two questions left. The first concerns CombiGene as a company. What you present here means, if I understand correctly, that CombiGene increases its ambitions quite considerably when it comes to the future of the company. Have you started preparing to handle a much larger project portfolio?

"Absolutely. Last spring, we hired Alvar Grönberg as Senior Program Director and recently we recruited Peter Ekolind to the position as Chief Operating Officer and Birgitta Ståhl as Senior Director In-licensing. Birgitta will be very active in the work of bringing in new projects and by Peter taking over some of my tasks, I will also have more time to work with different aspects of CombiGene's business development."

Then my last question. Despite being a small company, CombiGene has managed to attract highly qualified people with solid doctoral education and long experience from significantly larger companies. What is your secret?

"I don't know if we have any particular secret, but I think there are two things that make CombiGene an attractive company to work in. Firstly, gene therapy itself holds many fantastic opportunities and if there is one thing that characterizes CombiGene as a company, it is that we are passionate about helping people affected by life-changing diseases that today lack effective treatments. Our other advantage, I think, is the size of the company. There are absolute advantages of working in a large organization with all the resources available. At the same time, you have much greater opportunities to influence development and direction if you work in a smaller and more agile company. At CombiGene, the path from idea to decision is very short and we all strive to help people affected by severe life-changing diseases opportunities to get a better life through innovative gene therapies."

"We are passionate about helping people affected by life-changing diseases."

This interview was first published in its entirety by BioStock on September 30, 2022.

CombiGene's new COO wan building a large gene therapy

Peter Ekolind, previously Nordic Manager at Getinge Group, is the new Chief Operating Officer of gene therapy company CombiGene. BioStock contacted Ekolind to learn about his ambitions for the company, as well as how he views a potential broadening of the company's portfolio.

CombiGene's drug candidate CG01 is being developed as a new treatment for drug-resistant focal epilepsy, a disease that affects approximately 47,000 patients annually in the US, EU4, UK, Japan and China. Today's treatment options are limited to relieving symptoms without addressing the root causes of the disease, and they require lifelong administration. CG01, on the other hand, aims to cure the disease after only one or a couple treatment sessions.

CombiGene's new COO comments

This week, Peter Ekolind took up the part-time role of Chief Operating Officer at CombiGene, with responsibility for the company's operational activities.

Peter, can you talk about your professional experiences?

"I have worked within the life science sector for most of my professional life. For the first 15 years, I was active in the pharmaceutical industry in Sweden and Norway, mainly within sales, marketing and management. In 2001, I switched to medtech when I became CEO and Nordic Manager of Getinge Sverige AB. Since then, I have worked as CEO in smaller entrepreneurial companies such as Airsonett and the start-up company Avidicare. In recent years, I have worked as COO at Xintela on a consulting basis."

What made you interested in the role as COO of CombiGene?

"More recently, I have become increasingly focused on companies that are active in cell therapy and genetic engineering. Xintela focuses on stem cells and targeted cancer therapy, while CombiGene invests in gene therapy, which today is an expansive and dynamic area. I believe that there is a huge opportunity in treating severe, painful and currently incurable diseases by "helping" the body along the way, with, for example, gene therapy. CombiGene's business model is interesting, and, through the agreement with Spark Therapeutics for the epilepsy project, the company shows that it has a well-developed ability to sign agreements with Big Pharma companies. When CombiGene started looking for a COO, I became interested in the challenge and applied for the job."

Based on your experience, how do working methods and structures differ between larger global pharmaceutical companies compared to smaller and perhaps more agile biotech companies such as CombiGene?

"In many ways, of course. Resources in terms of staff and budget is an obvious difference, but the size of the global pharmaceutical companies also leads to development taking time, sometimes a very long time. What CombiGene lacks in resources can, to some extent, be compensated for by speed in decision-making and pace of development, which also applies to decisions on issues such as in-licensing of new projects."

CombiGene's current business focus is to expand and inlicense additional gene therapy projects. How do you look upon the significance of this process?

"It is central to the company. The business model is based on CombiGene being able to identify and attract new gene therapy projects at an early stage where there is a commercial business opportunity. To succeed in this, a competent and active team is required. I've already gotten to know the team and look forward to working with them."

Looking ahead, in what ways do you want to be involved in developing CombiGene's operations in a couple of years' time?

"In a few years' time, I envision that there is a larger and broader portfolio of gene therapy projects in the company. With more projects comes the need for an increasingly larger organization and, with my background, I will be able to contribute to the development of the company. A continued recruitment of the right skills will be crucial for the company's future development."

"In a few years' time, I envision that there is a larger and broader portfolio of gene therapy projects in the company."

nts to be involved in y company

Birgitta Ståhl, CombiGene's new Senior Director In-licensing

About the importance of balancing risks and opportunities

Earlier this autumn, Birgitta Ståhl joined the CombiGene team as the company's Senior Director In-licensing. Birgitta will thereby have a central role in CombiGene's efforts to find new projects that may be interesting for in-licensing. Ingeneious contacted Birgitta to talk about her work and how she looks at the fact that all drug development takes time, costs large sums of money and that there is a significant risk that a project does not reach all the way to market.

Welcome to CombiGene and Ingeneious! Can you tell us a little bit about youself?

"Thank you! I have a degree in pharmacy from Uppsala University and an MBA from the University of Westminster in London. I have worked many years in the life science industry in all stages of drug development. I come most recently from Oncopeptides AB where I was Global Project Director. Previously, I worked in Karolinska Development's portfolio companies and held various positions at Novartis and Pfizer. I hope to be able to use the broad experience and knowledge I have accumulated in life science as I now look for and evaluate new projects for in-licensing."

All drug development takes time and is very costly. In addition, there is always the risk that a project will not reach market approval. How do you see this?

"There are, as you say, significant risks in all drug development. The question is how to deal with this fact. From a business point of view, there is one component of the costs and risks you mentioned. The second component is made up of the potential revenue from drugs that make it all the way to market. All pharmaceutical companies need to balance these two components so that over time the revenue component outweighs the cost and risk component. A little philosophically, it can be said that it is important to identify and remove those projects that do not have the conditions to reach all the way to market as early as possible. To phase out unviable projects early on should not be seen as a failure, it is on contrary the basis of what we call portfolio management. The sooner you can do this, the less resources you have expended."

"Our ultimate goal is to develop therapies that can decisively improve the lives of people affected by severe life-changing diseases. The more efficient we can focus our resources on viable projects, the better the chances are that we actually succeed!"

"Our ultimate goal is to develop therapies that can decisively improve the lives of people."

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, info@fnca.se.

CombiGene

The gene therapy explorer

CombiGenes vision är att ge patienter som drabbats av svåra livsförändrande sjukdomar möjlighet till ett bättre liv genom nya genterapier.

www.combigene.com