

# INGENEIOUS

NEWS FROM COMBIGENE AB

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CombiGene establishes collaboration with Danish company Zyneyro to revolutionize the treatment of chronic pain

INTERVIEW WITH COMBIGENE'S CEO JAN NILSSON

# A unique opportunity for CombiGene and Zyneyro to reduce pain in the world

● *CombiGene's cooperation agreement with Zyneyro has just been made public when Ingenieous manages to reach CEO Jan Nilsson for a telephone interview about the latest addition to the company's project portfolio. The intense buzz in the background reveals a good atmosphere and high energy at CombiGene's office in Lidingö.*

## There seems to be a good atmosphere at CombiGene.

Jan laughs before answering. "There really is. We are very happy about the cooperation agreement with Zyneyro. This is a very important day in CombiGene's history. Together with our new colleagues at Zyneyro, we now have the opportunity to develop therapies for the treatment of severe pain, a real scourge for large parts of the world's population. It is also very satisfying to be able to state that we have been successful in our efforts to find and in-license a new and extremely interesting project."

## What made you interested in this particular project?

"A lot of things! First, pain is a gigantic problem. Estimates show that between 15-25 percent of the adult population in Europe and the United States suffers from ongoing pain problems and about 7 percent have chronic pain. The need for new and effective therapies is thus enormous. Today's alternatives are in many cases not very effective and have a number of drawbacks. The problem is that they are not specifically developed to treat chronic pain and the pain relief achieved often has a number of disabling side effects such as depression, anxiety, fatigue, impaired physical and mental ability, and addiction problems. In the United States, an estimated 700,000 people have died due to opioid abuse in the past 20 years. It would be fantastic if we at CombiGene, together with our Danish partner Zyneyro, could be part of a future solution to the problems caused by pain."

## How do you view the development that Zyneyro has been pursuing?

"I'm incredibly impressed! Our colleagues at Zyneyro have developed a unique concept to offer effective pain relief without the side effects that today's treatments often give rise to. The development program consists of two drug candidates: a peptide treatment and a gene therapy treatment. The peptide treatment is intended to be used in severe temporary pain conditions, while gene therapy treatment is being developed to treat severe chronic pain conditions. What has impressed me the most is precisely the combination of two therapies that address both temporary and chronic pain. The idea of also being able to use the peptide treatment as a screening opportunity for a possible AAV treatment makes the concept even stronger."

## How far has the project come?

"Both drug candidates are in preclinical phase and there are still several preclinical studies before the project can proceed to studies in humans."

## How far is it to market?

"It's virtually impossible to have a clear idea of that right now, so let me turn the perspective around a little bit. The development program that we will run together with Zyneyro includes two treatment methods, a peptide treatment, and a gene therapy treatment. I believe that with the peptide treatment we will have the opportunity to

initiate studies in humans, so-called clinical phase, in 2025 if everything goes according to plan. As for the gene therapy treatment, clinical studies in humans will be able to begin some years after that. Like all drug development, this development program also contains several elements of uncertainty and will take significant time even if everything goes exactly according to plan."

## How do you assess the commercial potential?

"Given that the problem of chronic pain is so great, there is of course also great commercial potential. The study "Pain in Europe" estimates the costs to society at 3-10 percent of gross domestic product. In the US, the yearly cost of pain relief is estimated at USD 560-6352 billion. The need for, and hence the market for, an effective pain relief treatment is thus great."

## Does the agreement with Zyneyro mean that you are now putting your efforts to find additional projects on hold?

"Not at all. This work will continue unabated. Our ambition is to build a broad portfolio of projects in different phases of drug development, ranging from projects in the really early phase to projects in pre-clinical development and thereby contribute to gene therapies being put to clinical use."

*"It would be fantastic if we at CombiGene, together with our Danish partner Zyneyro, could be part of a future solution to the problems caused by pain."*

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THEME PAIN

# Some facts about pain

● Pain is a complex area, not least because there are several different types of pain, and that pain can have many different causes. Pain also contains major complex of problems and can more or less take over everyday life for those affected. Existing treatments have a variety of side effects.

Pain can occur, among other things, at high heat or at pressure or impact. Such pain is called nociceptive pain or tissue injury pain. In some situations, the body may have difficulty localizing the pain. It can then manifest in another body part, and you then talk about referenced pain. An example of this is a heart attack where the pain can radiate into the left arm.

Pain can also occur in injuries or diseases of the nervous system itself, both in the peripheral nervous system (PNS) and the central nervous system (CNS). Even psychiatric diseases can give rise to pain, so-called psychogenic pain. There are also pain conditions where you do not know the cause, you then talk about idiopathic pain.

The pain that CombiGene and Zyneyro intend to treat are severe chronic pain conditions such as neuropathic pain, phantom pain and pain associated with various types of back injuries where the pain is caused by an increased sensitivity in the nerve pathways.

### Pain is a major global problem

Between 15-25 percent of the adult population in Europe and the United States suffers from ongoing pain problems and about 7 percent have chronic pain. In the United States, between four and eight percent of the population is estimated to be affected by high impact chronic pain. Conventional treatment consists mainly of anti-inflammatory drugs, antidepressants, antispasmodics, and opioids (a group of substances with a morphine-like mechanism of action).<sup>1</sup>

### The problems with today's treatments

The problem with these treatments is that they are not specifically developed to treat chronic pain. The pain relief that is achieved therefore often has a number of disabling side effects such as depression, anxiety, fatigue, impaired physical and mental ability, and addiction problems. In the United States, an estimated 700,000 people have died due to opioid abuse in the past 20 years.

### Pain affects everyday life

Living with constant pain is incredibly tiring. Long-term/chronic pain risks to completely dominate life with limitations in mobility and daily activities and inability to work with a low quality of life and a negative social situation as a result. It is not uncommon for pain problems to lead to stress, sleep problems, depression, and anxiety, which in turn can enhance the pain experience.

<sup>1</sup>Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016; CDC; Morbidity and Mortality Weekly Report Weekly / Vol. 67 / No. 36 September 14, 2018

Sources:

- <https://sv.wikipedia.org/wiki/Smärta>
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# What does pain cost – really?

● Pain costs a lot in the form of daily human suffering. There are also great financial costs linked to long-term pain conditions. What does the pain cost society if you include the cost of care, rehabilitation, and sick leave?

For society, the number of patients with long-term pain puts a huge strain on the healthcare system in the form of doctor's visits, physiotherapy, psychological treatment, and workplace-related adaptation/training. Reduced working capacity to varying degrees leads to lead to large production losses for society.

SBU (The Swedish National Agency for Medical and Social Evaluation) has estimated the cost to Sweden at a total of approximately SEK 87.5 billion for the year 2003. Of these, SEK 7.7 billion were direct health-care-related costs for visits to doctors and other health-care providers, as well as medicines. The majority of the costs of approximately SEK 80 billion, or >90% of the total cost, are due to indirect costs, i.e., loss of production as a result of illness-related absence from work. 40 percent of all visits to primary care occur due to pain.

In the United States (2010), the annual total cost of chronic pain is estimated to be between USD 560-635 billion. By comparison, the corresponding cost for heart disease amounts to USD 309 billion and for cancer USD 234 billion

The study "Pain in Europe" estimates the costs to society at 3-10 percent of gross domestic product.

Sources:

- Gaskin DJ, Richard P: The economic costs of pain in the United States. *J Pain* 2012, 13:715-724.
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INTERVIEW WITH ZYNEYRO'S CEO PETER HORN MØLLER

# 20 years of research have led to a potentially groundbreaking pain treatment

● *Zyneyro was founded by a group of researchers from the Department of Neuroscience at the University of Copenhagen and a group of entrepreneurs who together have extensive experience in all aspects of early drug discovery, development, and entrepreneurship. The company's researchers have worked to understand the ability of the brain and nervous system to adapt to the influence of the surrounding environment. Zyneyro's goal is to translate this knowledge of modulation of neuronal interaction into developing a number of drug candidates. Ingeneious contacted Zyneyro's CEO Peter Horn Møller for an interview about the pain program and the company's collaboration with CombiGene.*

## **How did you discover the biological mechanism of action that forms the basis for the pain program?**

"The word discovery gives you an idea of a eureka moment, where the insight hits from one moment to the next. In reality, "the discovery" was a process for almost 20 years, in which professor Ulrik Gether, associate professor Kenneth Madsen and associate professor Andreas Toft Sørensen focused on developing the right substance that allows us to block a certain protein (PICK1) involved in the development of chronic pain, including so-called neuro-pathic pain, which is seen after spinal cord injuries, amputations (phantom pain) and surgeries. In the process, they tested many strategies and we occasionally ended up in dead ends, and the fact that the three researchers have come up with two strategies with great therapeutic potential we regard as the sum of these experiences. I specifically remember when the three researchers told me about the moment they received a call from our partner Christian Bjerggaard Vægter in Aarhus, who was the first to test the drug candidate in a pain model in mice. Christian didn't have time to say his name, he just asked what on earth we had concocted, because it completely alleviated the pain symptoms in his mouse model. From that moment on, it was clear that we had made a groundbreaking discovery. Since then, we have spent nearly five years further developing and qualifying the drug candidates to the current stage, where they are ready for a focused drug development process."

## **Why is this field of research so interesting?**

"Chronic pain affects countless people in a completely inhumane way. Unfortunately, chronic pain is very difficult to treat with existing drugs. Often you have to resort to opioids (morphine and morphine-like drugs) that are highly addictive and require higher and higher doses. This has led to the so-called opioid crisis in the United States, where there has been a dramatic increase in opioid abuse and related deaths. There is thus a basic need for better painkillers."

## **What makes the concept unique?**

"Several things. First, our scientific team is the group in the world that knows most about the biological target that is at the heart of our concept, PICK1. We have been working on PICK1 and PICK1's role in pain for the past 20 years at the University of Copenhagen."

Continued in the next post ▶

*"From that moment on, it was clear that we had made a groundbreaking discovery."*



Photographer: Jakob Bostrup

## INTERVIEW WITH ZYNEYRO'S CEO PETER HORN MØLLER

## “We have an exciting journey ahead of us before we have drug candidates ready for clinical trials in humans.”

Among other things, we have found that PICK1 regulates a special receptor that is of central importance for the development of chronic pain. Unfortunately, you cannot block this receptor directly due to life-threatening side effects. However, PICK1 is required to move this receptor to the surface of patients' nerve cells and our approach is to block PICK1, thereby ensuring that the receptor does not come to the surface of the cell at all. This is a unique principle and has been shown to be exceptionally effective in relieving chronic pain in our animal models. Our data show that we can eliminate the pain and restore normal sensitivity without the usual side effects and without creating addiction. This is actually groundbreaking in itself. At the same time, we have developed a therapeutic variant, which can be given as gene therapy, where the body itself produces the drug. This means that you ultimately only need one treatment to potentially achieve lifelong pain relief. All in all, this will be life-changing for the many millions of pain patients who today for which there is no effective treatment available.”

### Why did you choose CombiGene as your partner?

“One of the inventors behind the technology, Andreas Toft Sørensen, had a number of academic research projects in collaboration with CombiGene that were not about pain, and one day Andreas asked me if we should arrange a meeting with CombiGene. The atmosphere and dialogue at the first meeting were exceptionally open and constructive and just a few weeks after the first video meeting (during the COVID-19 misery) we started discussing a potential collaboration – and then negotiations began on the form of this cooperation.”

“At that time, we had a number of dialogues with other industry partners and investors, but we quickly came to the conclusion that we in CombiGene had met the optimal partner for this project. CombiGene and Zyneyro share the same basic approach to partnerships, and we are pleased that the collaboration with CombiGene is based on values such as trust, mutual respect, and focused work. In addition, CombiGene has a highly experienced drug development team that builds on and complements Zyneyro's very strong competencies in the early drug development phase.”

“In collaboration with CombiGene, Zyneyro will have unique access to potential partners within Big Pharma with the resources and expertise to take the drugs to patients – in addition to the partners Zyneyro has been in contact with.”

### How do you view the future?

“We have an exciting journey ahead of us before we have drug candidates ready for clinical trials in humans. Together, we have a well-composed team with the ability to reach the goal as quickly as possible – it is very motivating. The fact that we have already created a good climate of cooperation between Zyneyro and CombiGene means that it will be a fun and inspiring journey – this is also important to us.”

*“Our data show that we can eliminate the pain and restore normal sensitivity without the usual side effects and without creating addiction.”*



# Pain veteran assisted CombiGene with the evaluation of the new development program



Odd-Geir Berge

● *Odd-Geir Berge has previously, among many other things, worked as a Senior Principal Scientist, Analgesia at AstraZeneca's research department in Södertälje. He now works as an independent consultant at OGBConsulting AB. Odd-Geir Berge has been involved in CombiGene's evaluation of the project. Ingeious contacted him for an interview regarding CombiGene's newly established collaboration with the Danish company Zyneyro.*

## **How did you first come into contact with the CombiGenes/Zyneyro pain program?**

"I got a call from Karin Agerman, CombiGene's Chief Scientific Officer, who knew that I have a consulting business in the area of pain. Karin and I know each other from AstraZeneca. Both the project and the form of collaboration that Karin suggested were so interesting that I could not but say yes when she proposed a consulting assignment."

## **You yourself have extensive experience from working with pain relief. What would you say are the biggest challenges?**

"We know quite a lot about different mechanisms that contribute to acute and chronic pain, but how the mechanisms interact we know less about. It is therefore a challenge to understand how important a specific mechanism is for clinical pain and whether it can be used for pain relief without problematic side effects. In addition, we depend on animal models with limitations that must be understood in order for us to interpret the data correctly. The overall challenge will be to translate between the different levels of the research process - from disease mechanisms in patients to biochemical processes that can be studied in the laboratory, and back via various animal and early studies in humans and finally to the patients who are the target of the treatment."

## **How would you like to comment on the CombiGenes/Zyneyro pain program?**

"Chronic pain is a major medical problem where good treatment is lacking for large patient groups. Existing drugs have limitations when it comes to pain relief and often have unacceptable side effects. The need for new forms of treatment is therefore great. The current project is based on a new concept with extensive scientific support, including data from animal models. In the CombiGenes/Zyneyro concept, the pain can be attacked in two ways that complement each other: firstly, with a peptide with a shorter effect and secondly with a gene therapy that opens up the possibility of a lifelong effect. Patients with different needs would thus receive optimally adapted treatment. Being able to increase the likelihood of a successful gene therapy treatment by using the peptide as a screening method is extremely interesting. This is a promising project that gives hope for significant therapeutic progress."

# Alvar Grönberg wants to become pain's enemy number one



● Alvar Grönberg is Senior Program Director at CombiGene. He has a PhD from Karolinska Institutet (KI) in Stockholm and many years of experience from both academia and the international pharmaceutical industry, including senior positions at companies within Karolinska Development and Abliva AB. Alvar's competencies include a deep knowledge of peptides, which makes him an ideal person to lead the pain program on the part of CombiGene.

Genevägen contacted Alvar to hear how he views this major task and how he views the possibilities of the project.

**You have a doctoral thesis from KI and long experience from work in both academia and industry. What motivates you in your work?**

"It is first and foremost to be involved in developing new drugs to treat severe diseases. Being involved in leading the development process in a drug program, planning studies, interpreting data, and experiencing successes is very stimulating. As everyone in the industry knows, you also suffer from setbacks and sometimes run into problems, but even that is motivating, especially when you despite the difficulties find a way forward. When it comes to drug development, the work often borders on research and scientific issues, which makes the work extra exciting and interesting."

**What experiences and knowledge will you benefit most from in your role as CombiGene's Senior Program Director for the new pain program?**

"It is all my previous experience of working with peptides and small molecules as well as my long experience of project management in drug development that I will benefit from. When it comes to the development of gene therapies, I am still learning, but here I will have a very good support and help from my competent and experienced colleagues."

**The pain program is being developed to offer effective pain relief without the side effects that today's treatments often give rise to, which has been made possible thanks to Zyenyro's**

**researchers identifying a new biological mechanism of action. What is your view on this aspect of the program?**

"The new mechanism of action is very exciting and provides effective pain relief without visible side effects, especially the risk of addictiveness, in the preclinical models that have been used. In addition, the peptide-based drug candidate, and thus the mechanism of action, is subject to a special evaluation in an ongoing program, sponsored by the U.S. government, to ensure both efficacy and absence of risk of addiction. This is potentially a very important support in the development process."

**Are there other parts of the project that are particularly interesting from your perspective?**

"Yes, the fact that the program consists of two parts. On the one hand, we will develop a peptide-based drug for repeated treatment that has the potential to reach a broad group of patients with temporary pain. Based on the same mechanism of action, we are also developing a gene therapy that is intended for a specific group of patients with very severe disabling chronic pain. Through gene therapy, you achieve a very long-lasting effect with only one treatment. The peptide-based drug will be ahead of the gene therapy in the development program and furthermore it could potentially be available to use as a test treatment to see if the gene therapy will work for a patient."

**One last question. How is your Danish?**

"Jeg har nogle gange svært ved at forstå og jeg kan ikke snakke dansk, men det skal nok gå fint alligevel. We use English just to be safe!"



 **combiGene**  
The gene therapy explorer

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

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