INGENEIOUS

NEWS FROM COMBIGENE AB

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CombiGene

The gene therapy explorer

EDITORIALS

Growing momentum in the pain program COZY

The pain program COZY, which we are developing together with the Danish company Zyneyro, is currently in a very intensive phase. After establishing a joint COZY organization with Zyneyro at the beginning of the year, we have worked hard with preparations for the preclinical toxicology program in the peptide project COZY01 with the ambition to make this project be ready for clinical studies within a few years.

Preparations for the preclinical program

The preparations include selection of CDMO and CRO partners, i.e., the company that will manufacture the material for the toxicological study, respectively the company that will conduct the study. Choosing the right partners is an extensive task that has long-term and important implications. We have also worked to establish a Scientific Advisory Board for the COZY program. The Board's main function will be to provide scientific review and advice. We are thus rapidly approaching the preclinical studies that will make COZY01 ready for the first study in humans.

Pain costs society huge amounts of money

Pain is one of the biggest challenges in healthcare. Severe chronic pain causes immense human suffering. The disease also leads to enormous costs for society. In the US alone, society's total costs (healthcare costs and indirect costs such as sick leave and loss of production) for pain are estimated at USD 635 billion each year . One factor that further complicates the picture is that conventional treatments (mainly anti-inflammatory drugs, antidepressants, anti-convulsant drugs, and opioids) are not specifically developed to treat chronic pain. The pain relief that is achieved often has a number of debilitating side effects such as substance abuse problems, depression, anxiety, fatigue, reduced physical and mental ability. In the United States, an estimated 700,000 people have died due to opioid abuse in the past 20 years.

Great interest in new treatment options

Against this background, it is not difficult to understand that there is an enormous interest in new forms of treatment that do not have the disadvantages of today's drugs. A good example of this is the independent evaluation of COZY01 that is ongoing at the National Institutes of Health (NIH) in the US, in a government-funded program (Preclinical Screening Platform for Pain, PSPP). COZY01 has passed the first level of three and has been selected to move on to the next level where the substance will be tested in different pain models.

Great interest from Big Pharma

That interest in next-generation pain relief is also great among Big Pharma companies was something Zyneyro's CEO Peter Horn Møller and I experienced when we visited BIO2023 in Boston in early June. This year, the congress gathered 14,000 participants and 5,000 companies.

The primary purpose of our participation in Boston was to present our joint pain program COZY to Big Pharma companies. CombiGene has previously successfully outlicensed the epilepsy project CG01 to Spark Therapeutics in a deal with a potential value of USD 328.5 million. Our ambition is, of course, to make a corresponding journey with the pain program. Having said that, I would like to point out that deals of this kind are complex processes that take a long time to bring to a successful conclusion. The process begins by establishing a relationship with the potential companies, something that BIO2023 provided good opportunities for.

Positive meetings at BIO2023

The meetings we had with Big Pharma are of course surrounded by secrecy, which means that I cannot name the companies we met or give any specific details about our discussions. What I can say is that we met with several large pharmaceutical companies that are looking with interest at our pain program. We will have a continued dialogue about the pain program with those we met at BIO2023, and we have the ambition to over time expand the circle of potential partners.

Our focus for the second half of 2023 is now to continue the development of the very important pain program COZY. We will also continue our work to find additional projects to in-license to build an increasingly strong CombiGene.

Jan Nilsson

CEO

[1] *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Appendix C. The Economic Cost of Pain in the US. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Washington (DC): National Academies Press (US); 2011*

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"We met with several large pharmaceutical companies that are looking with interest at our pain program."

Interview with Jonas Ekblom
Newly elected Chairman of CombiGene

At the Annual General Meeting on May 25, 2023, Jonas Ekblom was elected new Chairman of the Board of CombiGene. At the Annual General Meeting, Board members Gunilla Lundmark, Peter Nilsson and Per Lundin were re-elected and Malin Almgren was elected as a new member of the Board. CombiGene's Board of Directors thus has significant knowledge and experience from key areas for CombiGene's continued development such as research, development, business development, intellectual property, marketing, and sales, as well as finance and accounting.

Ingeneious contacted Jonas Ekblom to see how he, as newly elected Chairman of the Board, views the continued development of CombiGene.

Jonas, can you briefly describe yourself and your background?

"I have a PhD in experimental neurology, and I am an associate professor in pharmacology at Uppsala University. I have worked in biotechnology and pharmaceuticals for almost thirty years. A significant part of that time I have been active in the US, where I still have a strong network. For the past fifteen years, I have mainly worked with smaller drug development companies. Over the years, I have had the privilege of being involved in many successful projects, but ultimately it is perhaps mistakes and setbacks that have offered the most instructive experiences. Over the past ten years, I have participated in the board work of more than a dozen biotech companies in Sweden, Switzerland, and the United States."

In early 2023, CombiGene initiated a collaboration with the Danish company Zyneyro to jointly develop the pain program COZY. The program consists of a peptide treatment and a gene therapy. How would you like to comment on the science behind the pain program?

"The COZY program relates to a completely new pharmacological principle for pain relief. A major problem with several of today's drugs for pain relief is tolerance development, i.e., that continuous treatment requires increasingly higher doses of the drug to achieve reasonable pain control. Data from experimental models with the COZY substances indicate that there does not seem to be any reduction in the pain-reducing effect over time. I also find it attractive to have two different types of pharmaceutical therapies, as this gives the company the opportunity to diversify risk. We get two bingo cards instead of one!"

Problems associated with pain are one of the biggest challenges in healthcare today. How do you see the commercial potential of the COZY program?

"It is well known that severe chronic pain is a very big problem. For the individual, chronic pain involves enormous physical suffering and can also lead to negative social consequences. An ever-present pain can make it difficult to work and participate in a normal social life. Today's drugs are not developed to treat chronic pain and have a number of severe side effects, not least the addiction problems associated with the use of opioids. Chronic pain costs both healthcare and society huge amounts every year. All in all, this means that there is a very high demand for new therapies that do not have the side effects we see with today's treatments. It is too early to quantify the commercial potential of CombiGene's pain program, but if we are successful in our development and succeed in taking the pain program all the way to market, the economic upside will be very significant, to put it mildly."

The epilepsy project CG01 was outlicensed already in preclinical phase. Are CombiGene and Zyneyro planning a similar journey with the pain program?

"Absolutely! CombiGene's strategy is to develop drug candidates that target large patient populations to late preclinical phase/early clinical phase and then enter into collaborations with larger

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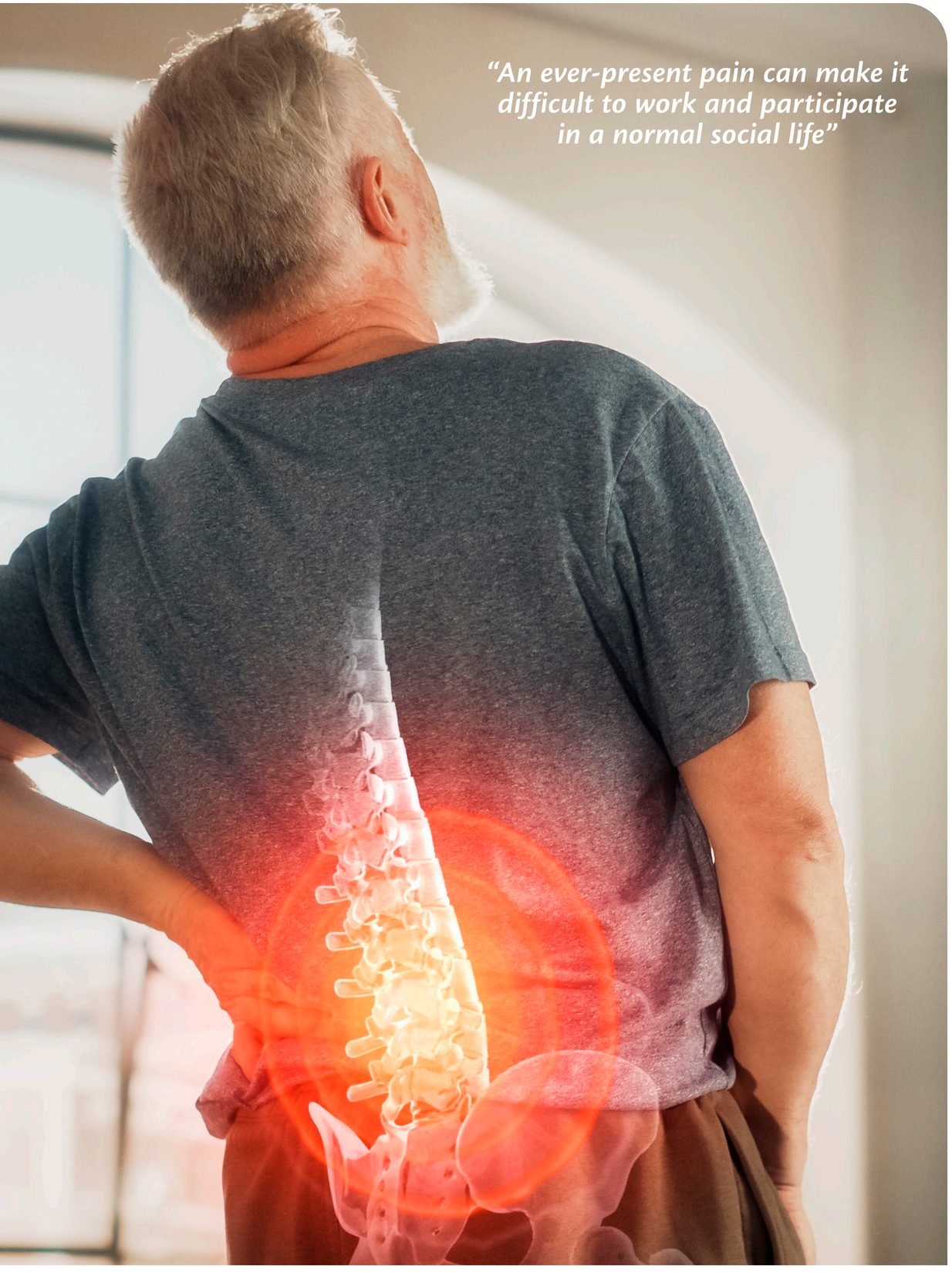

pharmaceutical companies. However, finding the right partner and negotiating favorable agreements takes a lot of time and it is important that this crucial work starts at an early stage. This is what we did with the epilepsy project CG01, and we have now initiated corresponding work within the pain program through the meetings and discussions that CombiGene's CEO Jan Nilsson and Zyneyro's CEO Peter Horn Møller had at the BIO Convention 2023 in Boston in early June."

In May 2018, CombiGene received a grant of EUR 3.36 million from the EU's Horizon 2020. The company then had two employees and one project in the early preclinical phase. Today, CombiGene is a significantly larger company with three projects that the company itself is developing and the epilepsy project CG01 outlicensed to Spark Therapeutics –one of the world's leading gene therapy companies. What milestones have been the most significant during this journey?

"We can start with one thing you mention in your question – the Horizon 2020 grant. This grant was an important part of the financing of the epilepsy project at the same time as it constituted a real quality stamp on CombiGene as a company. The choice of the most important service providers for the company's manufacturing chain has also been crucial. By choosing good service providers, we have significantly increased the chances for being able to successfully run several gene therapy projects in the same development phase. The in-licensing of the pain program COZY has the potential to be very important for CombiGene given the major problems that exist with today's pain treatment. The single most significant milestone for CombiGene so far is, of course, the licensing of the epilepsy project to Spark Therapeutics. This agreement has already provided CombiGene with USD 8.5 million and could potentially provide the company with an additional USD 320 million, excluding royalties. The agreement with Spark also meant a lot for CombiGene's reputation and made us an even more attractive partner in a number of different contexts."

CombiGene has the ambition to further broaden its project portfolio. Are there any particular disease areas that are particularly interesting – and if so, why?

"I would like to say that we have a broad outlook, but we have identified a number of projects that we are now evaluating to see if they could be of interest to us. These include diseases of the central nervous system, endocrine diseases, and genetic muscle diseases."

Why is it important that CombiGene broadens the project portfolio?

"All drug development takes a long time and the costs of developing a new drug are significant. If you look at the pharmaceutical industry as a whole, only a small percentage of all drug candidates reach the market. The reasons for this vary from that the drug candidate does not have the intended effect to that there are safety problems associated with the treatment. All drug development includes a preclinical phase where the drug candidate is evaluated in several different ways to ensure as far as possible that the drug is both effective and safe before initiating clinical development, i.e. studies in humans. However, success in the preclinical phase does not guarantee success in the clinical phase, it is often not possible to easily translate the results of preclinical experiments into efficacy in humans. It is therefore not uncommon to discover that a drug candidate does not meet the requirements for efficacy and/or safety when initiating the clinical phase. Having a broad project portfolio is important because it significantly increases the chances of reaching all the way to market. In a way, it's a bit like a football match. Not all chances result in goals, but the more chances you get, the more goals you will score."

Finally, how do you view the future of CombiGene?

"I am very positive about the future of CombiGene. Through the epilepsy project, the company has shown that it can take a project to a late preclinical phase and out-license it to a world-leading player – Spark Therapeutics was one of the very first companies to get a gene therapy approved for the US market. The first generation of gene therapy companies did not have the luxury of being able to purchase qualified services for the production of investigational drugs from external service providers. The first companies in this sector were therefore forced to build up and validate internal production capacity, which is associated with large investments. CombiGene, on the other hand, has had the opportunity to outsource all the steps in the manufacturing process externally, which means that we have very small overheads compared to many other gene therapy companies. The fact that CombiGene has a good reputation among colleagues in the industry is demonstrated, among other things, by the fact that CEO Jan Nilsson was recently appointed Chairman of the Board of the newly formed CCRM Nordic AB – a national cluster for the commercialization of advanced therapies. As Chairman of the Board of CombiGene, I personally look forward to playing an active role in the continued development of CombiGene!"

CombiGene's CEO Jan Nilsson elected Chairman of the Board of the newly formed CCRM Nordic AB

Advanced medicines – often called ATMP (Advanced Therapy Medicinal Products) – such as gene therapy and cell therapy have the potential to revolutionize the care of seriously ill patients. This task is, of course, not easy. It takes a wide range of expertise and resources to be successful. The Swedish government's stated goal is to make Sweden a leading nation in the field of ATMP. An expression of this ambition is the newly formed CCRM Nordic AB, which will coordinate a new national cluster for the commercialization of advanced therapies based on a successful Canadian model.

CCRM Nordic will establish a national infrastructure for the development, manufacturing, and commercialization of ATMPs, and will be available to stakeholders from academia and industry as well as the healthcare sector. The initiative has strong support from the industry with large Swedish ATMP organizations such as AstraZeneca, CombiGene, Cytiva, Getinge, Takara Bio Europe, TATAA Biocenter and Verigraft as well as local innovation actors such as GoCo Health Innovation City and GU Ventures and Sweden's innovation agency Vinnova.

The Chairman of the Board of CCRM Nordic AB is CombiGene's CEO Jan Nilsson.

Genevägen contacted Jan for a comment

"It is very honoring to have been elected Chairman of the Board of CCRM Nordic. Above all, I see it as recognition of the work that CombiGene has done over many years. Through the development of our projects, not least the epilepsy project CG01, we have gain solid competence in and extensive experience of the areas that CCRM Nordic will work with. We are very proud to be part of this very important initiative together with prominent colleagues such as AstraZeneca, Cytiva, Getinge, GoCo Health Innovation City, Takara Bio Europe, Tataa Biocenter and Verigraft," says Jan Nilsson.

CCRM Nordic meets the assignment from the Swedish government to establish a hub for the commercialization of ATMP and will complement and collaborate with existing public-private partnerships. CCRM Nordic will play an important role in laying the foundation for a thriving Nordic ATMP industry that will transform the outstanding research in the field into products that can change the lives of patients all over the world.

About CCRM Nordic

CCRM Nordic is a not-for-profit infrastructure for commercialization of advanced therapies based on the Canadian model and formed as a public private partnership backed by an industry consortium and the Swedish Innovation agency Vinnova. CCRM Nordic will accelerate commercialization of ATMPs and related technologies by providing specialized expertise and infrastructure. Our ambition is to collaborate with our Nordic neighbors as well as being part of the CCRM Global international networks of hubs. CCRM Global is an alliance of international hubs operating to coordinate and optimize opportunities in the field of cell and gene therapies and regenerative medicine-based technologies. The CCRM Nordic Board of Director members are starting with chair: Jan Nilsson, CombiGene; Lennart Johansson, Investor/Patricia Industries; Catarina Flyborg, Cytiva; Regina Fritsche Danielson, AZ; Carl-Peter Mattsson, GU Ventures, Michael May, CCRM.

ccrmnordic.se

CombiGene is very active at various types of conferences

CombiGene is very active at various types of conferences to keep abreast of the rapid scientific developments in the ATMP area, and also as part of the company's business development and communication with large investors. CombiGene is actively seeking new projects for in-licensing and the company has also initiated the long-term work to find a future partner within the pain program COZY. The company also participates in various events aimed at the stock market. As stated in CEO Jan Nilsson's editorial in this issue of Ingeneious, he, together with Zyneyro's CEO Peter Horn Møller, recently visited BIO2023 in Boston to present the pain program COZY to possible future Big Pharma partners. Other representatives of CombiGene have also been active at various conferences recently. Here's an overview:

"CombiGene's stated ambition is to in-license additional projects to build an increasingly stronger gene therapy company."

Interesting presentations and projects at ASGCT 2023 in Los Angeles

CombiGene's Chief Scientific Officer Karin Agerman and Senior Director In-licensing Birgitta Ståhl recently visited the ASGCT 2023 conference in Los Angeles, USA. ASGCT stands for American Society of Gene & Cell Therapy and is an organization of scientists, physicians, and patient advocates engaged in gene and cell therapy.

"The ASGCT conference is an important conference for CombiGene as its purpose is to present the latest findings in gene and cell therapy as well as new research and new indications that could be interesting in our efforts to further broaden CombiGene's project portfolio. This year's conference was a hybrid conference with a total of 8000 registered participants, of which 6600 were on site in LA," says Karin Agerman, Chief Scientific Officer at CombiGene. "A conference of this magnitude is difficult to summarize given the large amount of information and data presented, but among the highlights from CombiGene's perspective were the focus on AAV-based gene therapy and the possibilities of making gene therapy more organ specific through improved vector design. Since CombiGene works with AAV vectors, this element was particularly interesting. Another hot topic at the conference was CRISPR (clustered regularly interspaced short palindromic repeats) which can be used to edit genes. This research area is developing rapidly, but still has major challenges that need to be solved before it can be widely used clinically."

Another major topic at the conference was the healthcare reimbursement system in the US. The current system is based on chronic care models where compensation for a wide range of illnesses is paid for a large number of payment occasions over a large number of years. Gene therapy turns this model on its head through its ability to offer a lifelong cure or recovery for a growing number of diseases through one or a few treatments. The cost of gene therapy is thus not spread out over time like today's treatments, something that current reimbursement systems are not yet equipped for.

"One interesting session I attended was about the combination of AAV-based gene therapy and immunotherapy to create a completely new treatment modality to fight cancer," says Birgitta Ståhl, CombiGene's Senior Director In-licensing.

"In addition to an intensive search for new knowledge, Karin and I also spent considerable time looking for new potential projects for in-licensing and we identified a number of interesting opportunities that we are now following up. CombiGene's stated ambition is to in-license additional projects to build an increasingly stronger gene therapy company," Birgitta concludes.

Many interesting talks at 4th Gene Therapy for Neurological Disorders Europe

CombiGene's Senior Program Director Alvar Grönberg has also been active in CombiGene's search for new knowledge and new projects. Alvar visited the 4th Gene Therapy for Neurological Disorders Europe in Amsterdam at the beginning of June. He sums up the conference as follows:

"The conference included many interesting talks covering a range of topics, from how to achieve cell-specific gene transcription to payers' expectations of gene therapy products. The conference provided a good update on the field and an opportunity to interact with people from academia and from other companies."

Meeting with potential investors

Biotech Hanse is a Swedish-German biotechnology association that aims to connect the biotechnology and life science sectors in Sweden and Germany. The main focus areas of the organization are bilateral events, collaborations, exchange of knowledge and networking opportunities. Biotech Hanse addresses companies in the life science and medtech field, venture capital, tech transfer offices and other providers of services in this field. The organization was founded in 2014 and is based in Stockholm.

In mid-June, CombiGene's Chief Operating Officer Peter Ekolind participated in a meeting arranged by Biotech Hanse. The meeting was sponsored by, among others, the German pharmaceutical companies Boeringer Ingelheim and Bayer and the Swedish innovation agency Vinnova. In addition to the usual networking with colleagues in the industry, Peter also had the opportunity to present CombiGene to the four investor organizations that were present.

Productive meeting with Spark Therapeutics

The CG01 team, from left to right: Peter Ekolind, David Dobry, Apara Oza, Pernilla Fagergren, Jean Pedagna, Esbjörn Melin, Liz Ramsburg, Juha Savola, Karin Agerman, Lawrence Moon, Barbara Terzic, Jan Nilsson.

CombiGene and Spark Therapeutics recently held a biannual joint steering committee meeting in Stockholm, Sweden, to make a detailed plan for the epilepsy project CG01 for the upcoming six months. The meeting was highly productive, and again proved that Spark is an ideal partner for the epilepsy project CG01.

The delegation of Spark was seven people strong, including Liz Ramsburg, Head of CNS Research at Spark and Co-chair of the CG01 project. CombiGene was represented by Jan Nilsson, CEO and Co-chair; Karin Agerman, Chief Scientific Officer; Pernilla Fagergren, Director Clinical Development; Esbjörn Melin, Scientist; and Louise Aspenberg, Chief Financial Officer.

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

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