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Pursuing Novel Treatment Strategies for Neurodegenerative Diseases

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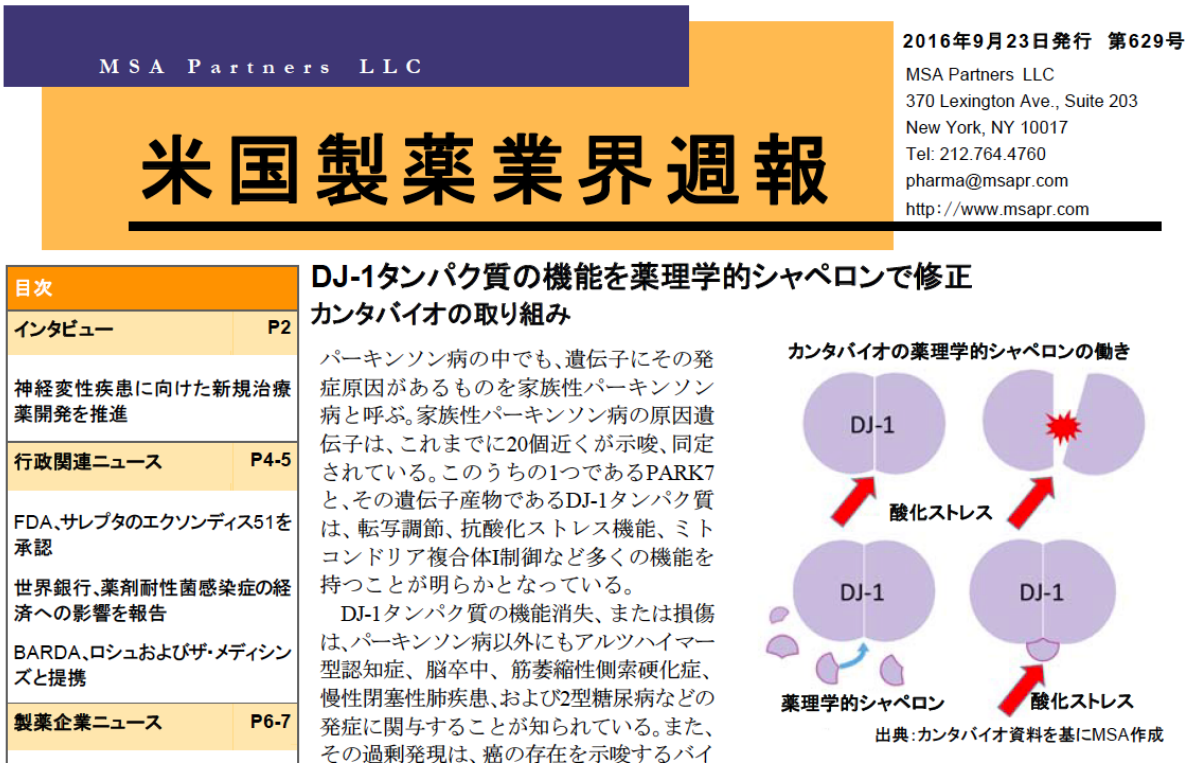

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DJ-1タンパク質の機能を薬理学的シャペロンで修正
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パーキンソン病の中でも、遺伝子にその発症原因があるものを家族性パーキンソン病と呼ぶ。家族性パーキンソン病の原因遺伝子は、これまでに20個近くが示唆、同定されている。このうちの1つであるPARK7と、その遺伝子産物であるDJ-1タンパク質は、転写調節、抗酸化ストレス機能、ミトコンドリア複合体I制御など多くの機能を持つことが明らかとなっている。

DJ-1タンパク質の機能消失、または損傷は、パーキンソン病以外にもアルツハイマー型認知症、脳卒中、筋萎縮性側索硬化症、慢性閉塞性肺疾患、および2型糖尿病などの発症に関与することが知られている。また、その過剰発現は、癌の存在を示唆するバイ

カンタバイオの薬理学的シャペロンの働き

出典：カンタバイオ資料を基にMSA作成

Based in Sunnyvale, California, Cantabio Pharmaceuticals is a preclinical stage biotechnology company focusing on developing and commercializing novel therapies for Parkinson's disease, Alzheimer's disease, and other related neurodegenerative diseases. We spoke with Dr. Gergely Tóth, the CEO, and Dr. Thomas Sawyer, COO, about the focus of Cantabio's research and its preclinical development programs.

Please describe the background to the establishment of Cantabio Pharmaceuticals.

Tóth: Cantabio Pharmaceuticals was started based on research that I had done at Elan Pharmaceuticals and the University of Cambridge on developing pharmacological chaperones. Our expertise is in identifying and developing pharmacological chaperones that target proteins that misfold and lose their function.

Please describe CB101 and CB102, your DJ-1-targeting small molecule pharmacological chaperones.

Tóth: One of our key targets is the DJ-1 protein, which, because of its ability to protect against oxidative stress and protein misfolding, is implicated in Parkinson's disease as well as Alzheimer's and other neurodegenerative diseases. Oxidative stress triggers the activation of DJ-1, which initiates a system-wide response to reduce oxidative stress and protein misfolding. In disease states, however, the protein becomes structurally damaged, thereby there is not enough functional DJ-1 to protect against the toxic effects of oxidative stress and protein misfolding. CB101 and CB102 are both small molecule pharmacological chaperones that are able to bind to DJ-1 and stabilize and modulate its activity to promote its protective role.

Sawyer: I would also like to point out the link between Parkinson's disease and the *DJ-1* gene, which is also known as the *PARK7* gene. When this gene becomes modified by a mutation the expressed DJ-1 protein is not properly folded and it ceases to function. This phenomena is linked to early-onset familial Parkinson's disease.

You are also developing a cell-penetrant DJ-1 protein that can cross the blood-brain barrier for Parkinson's disease and Alzheimer's disease.

Tóth: Yes, in terms of therapeutic R&D on DJ-1, our company is a global-leader as far as we know. There are a number of academic labs that have been pursuing significant and innovative research on DJ-1 drug discovery, such as Professor Hiroyoshi Ariga at Hokkaido University in Japan and Professor Soo Young Choi's laboratory at Hallym University in South Korea, which we follow and adopt.

With the cell-penetrant DJ-1 engineered protein, the idea there is to provide supplementation therapy. As I mentioned, in disease, DJ-1 loses its function. What we are aiming to do is to increase the level of functional DJ-1 in the brain of patients.

With this DJ-1 supplementation therapy, we are using very sophisticated technology to get proteins into the brain through a protein engineering process, in which we are fusing native DJ-1 with a small cell-penetrating peptide. We are gaining much experience from academic groups that have been pursuing this type of research to deliver proteins like DJ-1 into the brain, for example Professor Soo Young Choi's laboratory at Hallym University in South Korea.

Recently you announced a licensing agreement with the University of Cambridge for intellectual property on small molecules targeting the Tau protein for Alzheimer's disease.

Tóth: This program strategically fits into our pharmacological chaperone therapeutic approach and programs. The Tau protein is a highly pursued therapeutic target for Alzheimer's and related neurodegenerative diseases. There is a lack of small molecule clinical programs targeting Tau, and thus we will the Cantabio is well positioned to develop clinical candidates from the program.

This program actually comes from my academic research work at the University of Cambridge, UK. I initiated this project at the University of Cambridge and collaborated with a team of

scientist there led by Professor Mandelkow at the Max Plank Institute in Hamburg and also scientist at Novalix in France and Elan Pharmaceuticals in the US. This research was originally funded by the Wellcome Trust under a larger grant called the Neurodegenerative Disease Initiative, and later we also had a pharmaceutical partner, Elan Pharmaceuticals.

You also mentioned that a number of academic labs are pursuing research on DJ-1. Are you collaborating with them?

Tóth: Yes, we currently have collaborations with a number of leading laboratories some of which we have already announced, such Dr. Jean-Christophe Rochet at Purdue University and Professors Velez-Pardo and Jimenez-Del-Rioat at the University of Antioquia in Colombia.

By the way, there are a number of excellent laboratories in Japan that have produced high impact research publication on DJ-1 biology, and disease mechanism and pathology, such as Professor Hiroyoshi Ariga's lab at Hokkaido University and Noriko Noguchi and Yoshiro Saito at Doshisha University. We hope to have the opportunity to work with these laboratories in the future.

Lastly, could you describe your partnering strategy?

Sawyer: On the academic side, it has been important for us to collaborate with labs that have expertise that complements our own. The partnership with Purdue University was very important in the early stages of the company because they had the know-how in cell biology to support and develop our DJ-1 therapeutic approach. The same is true with the University of Antioquia, which has specific areas of expertise in oxidative stress cell biology that is very important to us. One of the main things we accomplish with these academic collaborations is further validation of our therapeutic candidates. It has been important to us to see that the results from our experiments are reproducible in other environments.

Tóth: In addition to partnering with leading scientists from around the world, we are in active discussions with potential pharmaceutical partners. We have a portfolio of programs, and we believe that they are unique and should be attractive to potential pharma partners. Our strategy is to partner one of our programs at a fairly early stage to enable us to take one or two of our programs into clinical trials.

Profiles
Gergely Tóth, Ph.D., M.B.A.

In addition to his role as CEO of Cantabio Pharmaceuticals, Dr. Tóth is also affiliated with the Wolfson Brain Imaging Centre at University of Cambridge (UK) and with the Research Center for Natural Sciences at the Hungarian Academy of Sciences (Hungary) as the Head of the Research Group for Neurodegenerative Disease Drug Discovery. He is a scientist and a serial entrepreneur with a long-term focus on developing therapeutics for neurodegenerative diseases. He holds a Ph.D. from the Department of Biomedical Sciences at Creighton University (US) and an Executive M.B.A. from the Judge Business School at the University of Cambridge (UK). He was a post-doctoral fellow at the Department of Molecular Biology at the University of

California at Berkeley (U.S.). Dr. Tóth previously held various research roles in small and global biopharmaceutical companies in the U.S., where he mostly pursued drug discovery research for Parkinson's disease and Alzheimer's disease.

Thomas Sawyer, Ph.D., M.B.A.

Dr. Sawyer combines a background in academic research with 13 years of experience in entrepreneurship, consulting and private equity investment in sectors including biotechnology, IT, logistics and natural resources across the globe. Dr. Sawyer holds a Ph.D. in Life Sciences from the University of Glasgow, an Executive M.B.A. from the University of Cambridge and is a visiting lecturer on Corporate Finance at the University of Exeter (UK). Dr. Sawyer combines a strong technical background with business development, corporate finance and operations, and is an active mentor on the Accelerate Cambridge business accelerator program at the University of Cambridge.