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Bringing NHA HDAC6 inhibitors to the clinic for cardiovascular and neurodegenerative disorders

A focused research program to understand HDAC6 biology has opened opportunities to treat patients with unmet medical needs.

Chong Kun Dang (CKD) Pharmaceutical Corp. has become one of Korea's top pharmaceutical companies by investing more than 10% of its revenue into research and development (R&D). The spending has enabled the 81-year-old business to establish fully integrated capabilities spanning the entire drug lifecycle and world-leading expertise in HDAC6 biology.

CKD is developing non-hydroxamic acid (NHA)-based histone deacetylase 6 (HDAC6) inhibitors for non-oncology indications. CKD's NHA inhibitors address the limitations of hydroxamic acid (HA)-based compounds and, in doing so, open up new therapeutic opportunities. CKD-510, a first-in-class NHA HDAC6 inhibitor, has potential therapeutic impact for atrial fibrillation (AF). Treatment with CKD-510 restored the shortened APD_{90} in cardiac tissue from chronic AF patients and demonstrated in vivo efficacy in tachypacing-induced animal models. A phase 1 study of CKD-510 was recently completed.

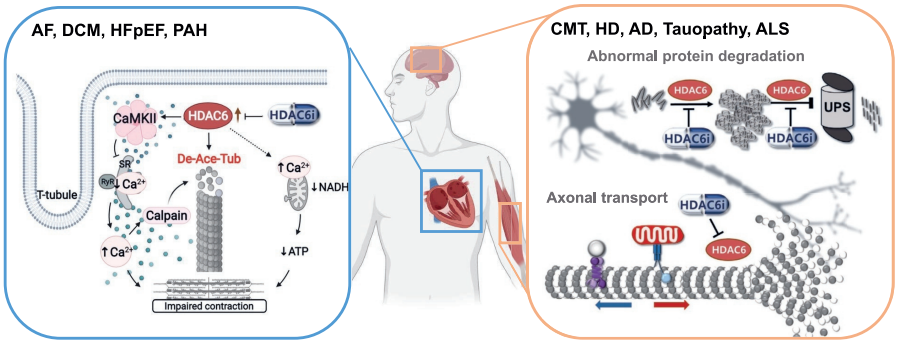

Fig. 1 | Therapeutic potential of HDAC6 inhibitor. HDAC6 is a key player in proteostasis and axonal transport. In cardiovascular diseases, HDAC6 inhibitor restores Ca^{2+} signaling and attenuates calpain/CAMKII by stabilizing microtubules (left). In neurodegenerative diseases, HDAC6 inhibitor corrects abnormal protein degradations and improves axonal transports (right). AD, Alzheimer's disease; AF, atrial fibrillation; ALS, amyotrophic lateral sclerosis; CMT, Charcot-Marie-Tooth disease; DCM, dilated cardiomyopathy; HD, Huntington's disease; HFpEF, heart failure with preserved ejection fraction; PAH, pulmonary arterial hypertension.

CKD's proprietary NHA HDAC6 platform

Based on the numerous scientific reports that link overexpression of HDAC6 to many diseased conditions, CKD began to work on a HDAC6 inhibitor program in 2010 and has remained active in the area, developing therapeutic agents for use in patients with cardiovascular and neurodegenerative disorders.

Concerns about HA-based HDAC inhibitors such as genotoxicity, rapid clearance and extensive metabolite formation, led CKD's research team to identify a series of NHA molecules that selectively inhibit HDAC6 without the downsides of HA-based drugs. In eliminating the shortcomings of HA-based drugs, CKD has introduced the possibility to use HDAC6 drugs in non-oncology diseases.

CKD-510, a first-in-class NHA for cardiovascular diseases

CKD is focusing on AF due to evidence that cardiovascular disease induces HDAC6 expression and thereby reduces tubulin acetylation. In preclinical animal studies, CKD-510 restored tubulin acetylation, normalized APD_{90}, and attenuated calpain and CaMKII levels, giving CKD confidence that the candidate is an excellent AF prospect that could control heart rhythm and improve structural problems associated with the disease (Fig. 1).

Current AF therapies include several ion channel blockers that have proarrhythmic potential by non-discriminating interactions with ion channels in the heart. Because CKD-510 does not directly inhibit ion channels, it is free from concerns associated with arrhythmia.

In a study of atrial tissue from AF patients, CKD-510 stabilized microtubules and normalized Ca^{2+} signaling, thereby restoring APD_{90} fully to the normal level. Dronedarone and vernakalant, multi-channel blocking AF drugs, restored APD_{90} partially, at best.

The APD_{90} normalizing effects of CKD-510 began to appear ten minutes after treatment. It is important to note that in the heart tissue study, APD_{90} did not increase above a normal range, even when high concentrations of CKD-510 were administered. CKD-510 is an effective potential treatment option for AF patients. In addition to AF, CKD-510 showed its therapeutic potential for other cardiovascular diseases including heart failure with preserved ejection fraction and dilated cardiomyopathy as well as pulmonary arterial hypertension.

Expanding the pipeline to neurodegenerative diseases

The research into the function of HDAC6 has also led to opportunities to use CKD-510 in other contexts, including the application to neurodegenerative diseases such as Charcot-Marie-Tooth disease (CMT)[1,2].

The axonal transport of intracellular vesicle and mitochondria is involved in many neurological disorders, including CMT. In addition, cytosolic protein aggregates have been considered as the main cause of various neurodegenerative diseases. Given that HDAC6 has been reported as a central regulator of both axonal transport and protein aggregates, the inhibition of HDAC6 has been considered as an important therapeutic strategy for neurodegenerative disorders (Fig. 1).

Upon treatment with CKD-510, axonal degeneration and impaired myelin were restored in the peripheral nerves of CMT model mice. Additionally, muscle atrophy was improved with increasing innervated neuro-muscular junctions and so were the defected motor behavioral and electrophysiological features. Moreover, the therapeutic potential was confirmed in CMT patient-derived neuronal cells.

People with CMT lack approved treatments, despite the condition being one of the most common hereditary neurological diseases. CKD-510 could address that unmet medical need by stopping axonal degeneration and improving motor function.

In addition to CMT, CKD is utilizing novel NHA inhibitors with sufficient brain exposure to other neurodegenerative indications such as Huntington's disease[3], Alzheimer's disease[4], primary tauopathies[5] and amyotrophic lateral sclerosis[6].

CKD is open to collaborations to support the progress of its HDAC6 science and pipeline programs.

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