Research Strategy: Björn Dahlöf

Epigenetic modulation in pulmonary disease

For decades, the treatment of pulmonary arterial hypertension (PAH) has focused on managing symptoms and physical capacity rather than addressing the fundamental pathology of the disease. Current therapies work through well-established pathways such as endothelin-1 antagonism, nitric oxide enhancement, prostacyclin analogues, and activin signalling inhibition.

While these approaches have somewhat improved outcomes, they have not been proven to reverse the structural changes that characterise PAH: the progressive thickening and narrowing of small pulmonary arteries that ultimately leads to right-sided heart failure and death.

Cereno Scientific's lead candidate, CS1, is a histone deacetylase inhibitor that works through epigenetic modulation to target the underlying mechanisms driving vascular remodelling. Rather than dilating vessels, we aim to restore their structural integrity by modifying gene expression patterns without changing the genetic code. This represents a potential paradigm shift from symptom management to disease modification.

The company's origins lie in a strong observation about tissue plasminogen activator. t-PA is a critical protein involved in the body's fibrinolytic capacity, and its expression is regulated epigenetically. Research by our founder Sverker Jern, professor of cardiovascular physiology at the University of Gothenburg, demonstrated that t-PA storage in the vessel wall decreases with age and disease, which increases thrombotic risk. Importantly, this could be reversed with valproic acid (VPA), an established antiepileptic drug with HDAC inhibitory properties.

Large observational studies from Denmark, the UK and Ireland showed that patients treated with VPA for epilepsy had 40 to 50 per cent fewer myocardial infarctions and strokes compared with those on other antiepileptic drugs. Experimental studies in humans at Sahlgrenska University Hospital demonstrated that VPA increased t-PA gene expression and protein production in both healthy individuals and coronary heart disease patients. This established a clear link between epigenetic modulation and thrombosis prevention.

Initially, we planned to develop VPA for thrombosis prevention. However, as a small biotech company, conducting thrombosis studies requiring tens of thousands of patients was unrealistic for a company of our size. During an extensive literature review in 2018 and 2019, we identified numerous cardiovascular indications where epigenetic modulation could have substantial impact. We found that HDAC inhibition showed remarkable effects in preclinical models of vascular remodelling, cardiac hypertrophy, fibrosis, and endothelial dysfunction in addition to the previously documented anti-thrombotic effects without bleeding.

PAH emerged as an ideal fit. The disease involves aggressive proliferation of cells in the pulmonary vasculature, with minimal apoptosis – behaviour reminiscent of tumour growth. HDAC inhibitors have shown success in certain cancers by reducing cell proliferation, and preclinical researchers working in pulmonary vascular disease had long advocated for HDAC inhibition as one of the most promising approaches for reversing vascular remodelling. However, most HDAC inhibitors were considered too toxic for anything beyond cancer treatment.

VPA presented a unique opportunity. It had been used safely in epilepsy patients for 50 to 60 years, was generally well tolerated, and had extensive safety data at doses higher than we intended to use. Moreover, it was one of the most extensively studied HDAC inhibitors in preclinical models of pulmonary vascular disease. When I informed leading researchers that we were bringing an HDAC inhibitor to clinical trials in PAH, their response was one of genuine excitement – they had long believed in the concept but thought it clinically impractical due to tolerability concerns.

PAH also offered practical advantages as an orphan disease. With approximately 192,000 patients globally treated in specialised centres, it was feasible for us to conduct trials and potentially market independently. This contrasted sharply with the thrombosis indication, which would require partnership with large pharmaceutical companies and substantially longer development timelines.

Cereno Scientific's lead asset, CS1, is an oral, controlled-release formulation of VPA designed to provide sustained HDAC inhibition. The drug works by modulating histone acetylation patterns in the cell nucleus, affecting gene expression in diseased tissue. In preclinical models, HDAC inhibition has demonstrated effects on multiple aspects of pulmonary vascular disease: reducing pathological proliferation, promoting apoptosis of abnormal cells, decreasing inflammation, and improving endothelial function as well as reducing pulmonary vascular resistance and blood pressure.

A particularly important finding involves plexiform lesions – complex vascular structures that are almost pathognomonic for PAH. These represent an escape mechanism where the body attempts to reroute blood past severely narrowed arteries. In the Sugen-hypoxia rat model, we observed dramatic, dose-dependent reductions in these lesions with our compound second HDAC inhibitor CS014, indicating substantial effects on vascular remodelling.

Our Phase 2a trial with CS1 in PAH provided encouraging exploratory efficacy signals. We observed improvements in right ventricular function, which is the most significant predictor of mortality in PAH, as well as disease risk scores, NYHA/WHO functional class and patient quality of life. Importantly, CS1 is designed as an add-on therapy to current standard of care, potentially offering disease-modifying benefits without replacing existing treatments.

CS1 is protected through three patent families in key markets into the 2040s, in addition to the US Food and Drug Administration-granted Orphan Drug Designation and Fast

Track designation, which recognises the unmet need and the potential for this approach. The European Commission has also granted Orphan Medicinal Product Designation. We are now preparing a Phase 2b global, multi-centre, placebo-controlled study to provide more definitive proof of concept, with plans to initiate in H1 2026.

While VPA offers substantial advantages, including decades of safety data, its status as a generic compound presents commercial challenges. We have therefore developed CS014, a deuterated analogue designed to retain all the beneficial HDAC inhibitory effects while improving the metabolic profile. VPA metabolism produces a rare but concerning toxic metabolite associated with hepatotoxicity, occurring in approximately one in 20,000 patients, mainly children. CS014 reduces formation of this metabolite by approximately 90 to 95 per cent.

In preclinical studies, CS014 has shown nearly identical HDAC inhibition curves to VPA, with particularly impressive effects in pulmonary hypertension models. The compound demonstrated strong dose-dependent reduction of plexiform lesions and reversed vascular remodelling and fibrosis. Importantly, CS014 has also shown robust antithrombotic effects across different vessel types – small arteries, large arteries, and veins – similar to VPA.

Cereno clinical trial

Cereno completed a Phase 1 trial of CS014 in healthy volunteers with top-line data published in July 2025. CS014 was safe and well tolerated at exposure levels that are expected to be sufficient, based on non-clinical data, to impact pathological pulmonary vascular remodelling and reduction of fibrosis, key drivers in several rare cardiovascular and pulmonary diseases. CS014 represents a patent-protected new chemical entity that maintains the therapeutic benefits we have observed with VPA while offering an improved safety profile. We have filed for patent protection and received approval in the UK.

One aspect of HDAC inhibition that distinguishes it from current PAH therapies is its disease-driven mechanism. Consider the contrast with prostacyclin analogues, which dilate vessels throughout the body, potentially causing systemic hypotension as a side effect. Or consider phosphodiesterase-5 inhibitors, originally developed for erectile dysfunction, which affect vessels beyond the pulmonary circulation.

HDAC inhibitors, by contrast, primarily affect tissues where HDAC expression is pathologically altered. The drugs target diseased tissue preferentially because that is where the aberrant gene expression patterns exist. This is conceptually like cancer therapy, where the effect is greatest in the tumour. The drug must pass through the entire circulation, but if vessels are not diseased, minimal effects occur.

This principle extends to our original observation about t-PA and thrombosis. The body's coagulation system is fundamentally a defence mechanism against bleeding. When vessel wall damage occurs, platelets accumulate and fibrin forms to prevent blood loss. The problem in modern cardiovascular disease is deficiency of t-PA, which is normally distributed locally at sites of thrombus formation to limit clot size and prevent vessel occlusion.

By increasing t-PA expression through epigenetic modulation, we restore this local regulatory mechanism. It functions like a building's fire suppression system whereby sprinklers activate only in the room where fire threatens, rather than flooding the entire building. Conventional antithrombotic therapies, in contrast, shift the entire body toward a more bleeding-prone state to prevent thrombosis.

The preclinical evidence supporting HDAC inhibition in pulmonary vascular disease is extensive. Hundreds of published studies demonstrate effects on vascular remodelling, endothelial function, cardiac hypertrophy, and inflammation across multiple experimental models. Many of these publications conclude with calls for clinical translation. Leading researchers in the field have described HDAC inhibition as potentially the most powerful approach they have observed for pulmonary vascular remodelling.

However, translating preclinical findings to humans presents inherent challenges. We can measure clinical effects – whether vessels dilate, whether heart function improves, whether disease progression slows – but the actual target engagement in the cell nucleus is difficult to assess in living patients. Unlike preclinical models where we can examine tissue directly, human studies must rely on surrogate markers and clinical outcomes.

For some relationships, such as the t-PA pathway in thrombosis, we have established clear connections from gene expression to protein production to clinical outcomes in humans. For other aspects of HDAC inhibition in PAH, we have strong preclinical evidence and encouraging early clinical signals, but more definitive human data are needed. Our Phase 2b study will incorporate more extensive biomarker analyses, including examination of blood cells, to better characterise target engagement and mechanism in patients.

We must also acknowledge that VPA, while one of the most studied HDAC inhibitors, affects multiple histone deacetylases rather than a single target. This lack of complete selectivity may be advantageous in a complex disease like PAH, where multiple pathological processes require modulation. However, it also means we cannot attribute effects to a single molecular mechanism with absolute certainty.

The fundamental question in PAH treatment is whether we can move beyond symptom and physical capacity management to actual disease modification and reversal of vascular remodelling. Current therapies have improved outcomes substantially, but patients still face progressive disease and premature mortality. The five-year survival rate, even with modern therapy, remains approximately 60 per cent and there is no cure.

Epigenetic modulation through HDAC inhibition offers a mechanistically distinct approach that addresses the underlying pathology. We are not simply dilating vessels or reducing pressure, but potentially restoring normal gene expression patterns and vascular structure. If successful, this could represent a fundamental shift in how we treat not only PAH but potentially other pulmonary vascular diseases.

This article was written by Dr Björn Dahlöf, chief scientific officer at Cereno Scientific AB.