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HypoxyStat, a small-molecule form of hypoxia therapy that increases oxygen-hemoglobin affinity

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SUMMARY

We have previously demonstrated that chronic inhaled hypoxia is remarkably therapeutic in the premier animal model of mitochondrial Leigh syndrome, the *Ndufs4* knockout (KO) mouse. Subsequent work has extended this finding to additional mitochondrial diseases and more common conditions. However, challenges inherent to gas-based therapies have hindered the rapid translation of our findings to the clinic. Here, we tested a small molecule (hereafter termed HypoxyStat) that increases the binding affinity of hemoglobin for oxygen, thereby decreasing oxygen offloading to tissues. Daily oral dosing of HypoxyStat caused systemic hypoxia in mice breathing normoxic (21% O_2) air. When administered prior to disease onset, this treatment dramatically extended the lifespan of *Ndufs4* KO mice and rescued additional aspects of disease, including behavior, body weight, neuropathology, and body temperature. HypoxyStat was also able to reverse disease at a very late stage, thereby serving as a clinically tractable form of hypoxia therapy.

INTRODUCTION

Oxygen serves as a substrate for over 200 biochemical reactions, making it essential for human health.[1] However, excess oxygen is also toxic.[2] We recently demonstrated that mitochondrial diseases reduce whole-body oxygen consumption, leading to an imbalance between oxygen supply and demand.[3–5] This imbalance results in tissue hyperoxia, as observed in the leading mouse model of mitochondrial disease, the *Ndufs4* knockout (KO) mouse. This model lacks an essential complex 1 subunit of the electron transport chain (ETC) and reproduces the pathology of Leigh syndrome, the most common pediatric mitochondrial disease. Similar findings of hyperoxia are evident in mitochondrial disease patients that exhibit elevated venous oxygen levels due to impaired tissue oxygen extraction.[6] Notably, we have shown that chronic exposure to inhaled hypoxia (equivalent to an altitude of 4,500 m) normalizes this tissue hyperoxia and dramatically extends the lifespan of *Ndufs4* KO mice.[3,5] Remarkably, this intervention can even reverse neurological lesions at the late stages of disease.[4]

Recent studies have further highlighted the therapeutic potential of hypoxia in mitochondrial disorders. For example, hypoxia has been shown to mitigate motor defects in a Friedreich's ataxia mouse model.[7] Additionally, our genome-wide CRISPR screen comparing hypoxia with normoxia identified over 75 additional monogenic disorders that could potentially benefit from hypoxia therapy.[8] Beyond inborn errors of metabolism, we recently demonstrated that chronic hypoxia alleviates many aspects of metabolic syndrome.[9] These findings align with epidemiological data showing a reduced incidence of cardiovascular disease, obesity, and diabetes in populations living at high altitudes.[10–18] Taken together, these results suggest that hypoxia may represent a therapeutic approach for a broad range of diseases, from rare genetic disorders to more common conditions.

Building on these discoveries, phase 1 clinical trials were recently completed to assess the feasibility of inhaled hypoxia therapy.[19] Patients were gradually acclimated to hypoxic conditions until they reached an arterial oxygen saturation (SaO_2) of ~85%. This exposure was well-tolerated, consistent with the fact that humans have resided at altitude for centuries.[20] Nevertheless, maintaining patients in a state of chronic hypoxia presents significant logistical challenges, underscoring the need to develop more practical approaches to hypoxia-based therapies.

Our previous research indicated that patients with mitochondrial disease would likely require continuous hypoxia throughout most of the day, making intermittent hypoxia or approaches such as "sleeping in hypoxia" insufficient.[4] Although relocating