From Cell Culture to Clinical Trials: Oxygen Microenvironments as Translational Determinants

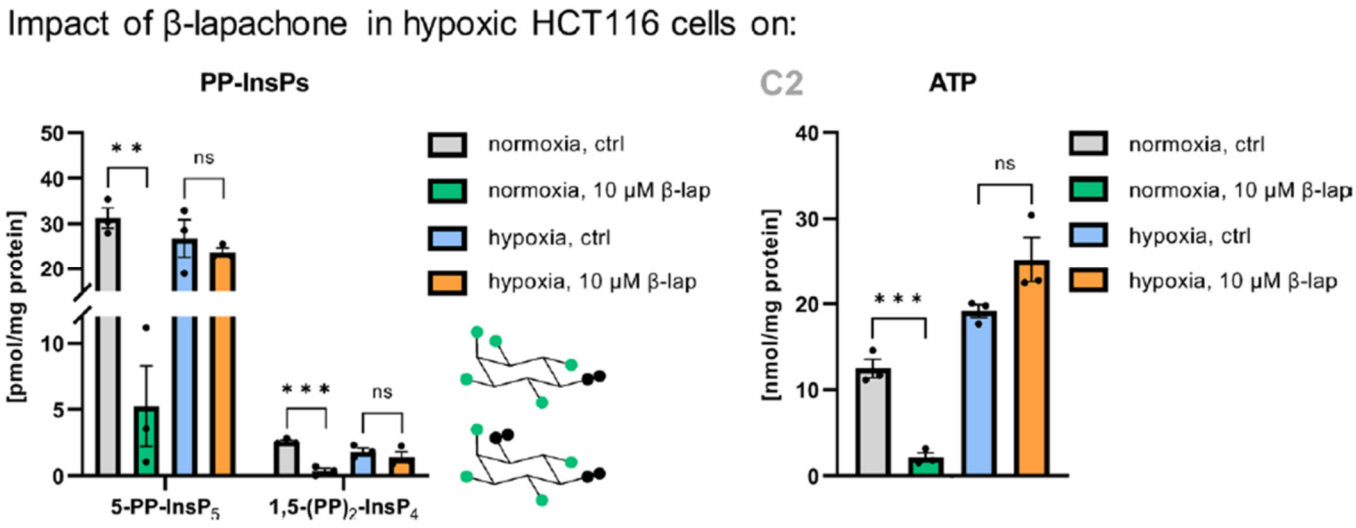
by Justin Croft

The challenges of translating research findings from cellular models to more intricate animal models or clinical trials are complex and multifaceted. Among the key factors that hold the potential to significantly enhance translational outcomes is the accurate emulation of *in vivo* oxygen microenvironments within cellular systems. This is especially relevant when evaluating compounds or therapeutics that are influenced by cellular oxygen availability such as Hypoxia-Inducible Factors (HIF) and Reactive Oxygen Species (ROS).

In this context, it becomes imperative to meticulously explore how genuine oxygen gradients within the physiological context might either modulate or constrain the expected mechanisms of action of a drug or molecule of interest. Intriguingly, despite its critical significance, the consideration of this dimension remains conspicuously absent in a substantial number of scholarly articles.

A recent publication in PNAS by Eisenbeis *et al.* (2023) entitled "**β-lapachone regulates mammalian inositol pyrophosphate levels in an NQO1-and oxygen-dependent manner**" exemplifies the importance of incorporating oxygen considerations when assessing translatability. The study aimed to unravel the intricacies of inositol pyrophosphates (PP-InsPs), molecules intricately linked to the oxidative stress response and performing diverse regulatory functions in mammals. The following finding, taken from the article, is particularly enlightening:

"Hypoxia completely abolished β-lap-mediated reduction of PP-InsP levels in HCT116 cells, which suggests that the quinone is affecting PP-InsP levels via ROS. The loss of potency of β-lap under hypoxia needs to be generally considered when results gained from regular cell culture experiments conducted under normoxia are applied to clinical trials: As physiological O2 concentrations [in the body] typically range from 1 to 10%, ROS-dependent β-lap toxicity shown in cellulo might be significantly reduced in vivo."



Courtesy of Eisenbeis et al. (2023)

The above study underscores the importance of incorporating oxygen-related considerations into experimental design, shedding light on the potential divergence between *in vitro* and *in vivo* responses. Scientists who meticulously account for the oxygen microenvironment stand to uncover nuanced insights, revealing that molecules or drugs exhibiting promising outcomes *in vitro* may manifest altered efficacy or safety profiles in the more intricate context of living organisms. As scientific inquiry continually evolves, acknowledging the role of

oxygen gradients in translational research emerges as a fundamental requisite for unraveling the full spectrum of biological responses.

It is worth highlighting the team's reliance on our advanced hypoxia workstation, the HypoxyLab, a cutting-edge technological solution that played a pivotal role in cultivating and sustaining their cell lines within tightly regulated oxygen environments. This platform not only facilitates extended periods of cell line growth under controlled oxygen, but also enables short-term experiments under conditions that closely mirror the *in vivo* microenvironment.

The HypoxyLab is an invaluable asset for laboratories striving to bridge the gap between cellular studies and the complexities of living systems. By providing a controlled oxygen atmosphere, this system empowers scientists to simulate physiological oxygen conditions, thereby enhancing the relevance and applicability of their research.