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The Next Revolution in Activity-Based Protein Profiling: Uncovering the Target of a 70-Year-Old Drug Leads to a Breakthrough in Female Biology and a Novel Therapeutic Strategy to Treat (Pre)Eclampsia and Other Deadly Neurological Disorders

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Hydralazine (HYZ, Apresoline®) is one of the oldest FDA-approved vasodilators with hydrazine pharmacophore (–NHNH2), initially introduced to treat malaria 70 years ago. HYZ was quickly repurposed as an anti-hypertensive, due to the prevailing yet unexpected side effect of lowering blood pressure. Even today HYZ remains in world-wide use to treat hypertension and heart failure. Despite decades of advancements in our physiological understanding of vasodilation, the molecular target(s) and mechanisms of action for HYZ remain entirely unknown. Although many other therapeutic options have proven superior in treating essential hypertension, HYZ still remains the most effective first-line treatment for preeclampsia, which is also poorly understood. Given this distinct clinical efficacy, identifying the target(s) of HYZ could not only categorize this unclassified vasodilator, but could also highlight novel drug target(s) for hypertension and suggest new therapeutic applications beyond the cardiovascular system and the kidneys – its role in the brain. We recently expanded our chemical proteomics discovery platform, termed reverse-polarity activity-based protein profiling (RP-ABPP) that exploits the unique reactivity of hydrazine pharmacophores to tag enzyme cofactors (e.g. metal, NAD, and FAD) and post-translational modifications (PTMs) in native biological systems, enabling us to profile and discover new enzyme functional groups of hydrazine MAOIs that are druggable by novel mechanisms using small molecules (Lin Z et al. ACS cent. Sci. 2021). This work led to an entirely new and unexpected off-target in the brain that we showed is related to important in neurotransmitter metabolism
Our RP-ABPP approach discovered the target of HYZ in cells and tissues, the specific inhibition of which explains the vasodilation mechanisms of HYZ and why it is effective in preeclampsia. Since this target has emerged as a promising therapeutic strategy for cancer and even other potential indications beyond the cardiovascular system, we initially applied HYZ to cancer cell lines and showed inhibited cancer cell growth by inducing cellular senescence, suggesting the potential for HYZ to be directly repurposed for cancer treatment as well as be further optimized (by our approach) for specific indications and improved safety and efficacy
In this presentation, I will review the target discovery story for an old drug that stands the test of time and has remained entirely dormant to any innovation of the 20th century until now.

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