Development of the first vascular-specific KATP channel inhibitor for the treatment of patent ductus arteriosus in newborns

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The ductus arteriosus (DA) is an essential fetal structure that shunts blood away from the high-resistance pulmonary circulation and toward the placental circulation, where fetal-maternal gas exchange occurs. Normally after birth, the DA undergoes vasoconstriction in response to increased arterial blood oxygen tension and secondary smooth muscle cell proliferation. The failure of the DA to close, or patent DA (PDA), is one of the most common congenital heart disorders, and its pharmacotherapy options are limited to non-specific medications that target prostaglandin pathways. ATP-regulated inward rectifier potassium (Kir) channels comprising Kir6.1 and SUR2B subunits are enriched in the DA compared to other vascular beds, suggesting they may represent novel drug targets for PDA pharmacotherapy. We hypothesize that inhibitors of Kir6.1/SUR2B will induce vasoconstriction and closure of the DA. Testing this hypothesis will require the development of highly specific inhibitors that can discriminate between Kir6.1/SUR2B and Kir6.2/SUR1 channels expressed in the pancreas and brain. We therefore performed a high-throughput screen of 47,872 compounds for novel modulators of Kir6.1/SUR2B. The most potent inhibitor discovered is VU0542270, which inhibits Kir6.1/SUR2 with an IC50 of approximately 100 nM and is highly selective for Kir6.1/SUR2B over Kir6.2/SUR1 and several other Kir channels. In pressure myography experiments on isolated mouse DA tissues, VU0542270 enhanced oxygen-dependent DA constriction in a dose-dependent manner. Future experiments will explore the binding site of VU0542270 on Kir6.1/SUR2B and the molecular mechanisms of its selectivity.