# CHRD 2024: Abstract Submission Form

**Presenter Name**
Saeid Maghsoudi

**Presenter Status**
PhD Student

**Role in the project**
Design
Perform Experiments
Analyze Data
Write Abstract

**Research Category**
Basic Science

**Title**
Selective Targeting of Adenylyl Cyclase Isoform 6: Exploring A Potential Treatment for Pulmonary and Cardiac Diseases

**Background**
cAMP is a crucial intracellular signalling mediator produced by adenylyl cyclases (AC isoforms 1-9). Although many drugs generating cAMP act on upstream GPCRs or downstream phosphodiesterases, ACs themselves have not been major drug targets. ACs are allosterically activated by forskolin (FSK). We reported AC inhibition by S-nitrosylation in pulmonary artery (PA) myocytes exposed to hypoxia. By mutational analysis we identified C1004, at the interface of AC6 with Gαs, as crucial to initiate AC6 activity. We hypothesized that hypoxic AC6 activity can be rescued by novel FSK derivatives targeting AC6.

**Objective**
To determine whether novel FSK derivatives targeting AC6 can rescue hypoxic AC6 activity.

**Methods**
Myocytes from newborn piglets, and HEK293 cells overexpressing AC isoforms (AC3, 5, 6, 7, 9) or cysteine-to-alanine mutants (AC6_C1004A, AC6_C1145A or AC6_C447A) were cultured in normoxia (21% O2) or hypoxia (10% O2) for 72 hours, or challenged with nitroso donor S-nitrosocysteine (CysNO). Cells were lysed for measurement of AC catalytic activity and protein S-nitrosylation. FSK-dependent cAMP generation was measured using a live-cell cAMP biosensor. A library of forskolin derivatives was synthesized and tested for activation of AC isoforms 3, 5, 6, 7 or 9, and in PA by isometric myography.

**Results**
AC6 catalytic activity is uniquely inhibited in hypoxia or by CysNO, stimulated with or without FSK; cAMP production in hypoxia is impaired which correlates with increased cysteine nitrosylation of AC6. Selective AC6 inhibition in PA myocytes extinguishes AC sensitivity to inhibition by hypoxia. Alanine substitution of C1004 decreases S-nitrosylation of AC6 and extinguishes hypoxia sensitivity of AC activity. Among compounds tested, FSK 1α,9α-carbonate offered relatively selective activation of AC6.

**Conclusion**
Although hypoxia inhibits AC6, forskolin can stimulate catalytic activity of AC6 under hypoxic conditions. Selective AC6 reactivation is a promising therapeutic target in pulmonary and cardiac diseases.

**Do you have a table/figure to upload?**
No

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