Pharmacologic Induction of Tolerance for Hypoxia and Hypothermia (PhIT HyHo)

Results to Date
Proposed Next Steps

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Affiliations and Related Information

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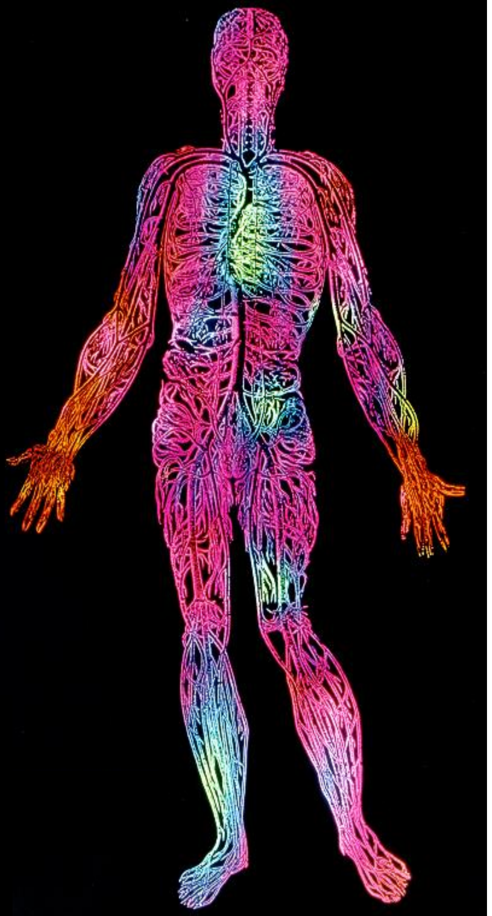
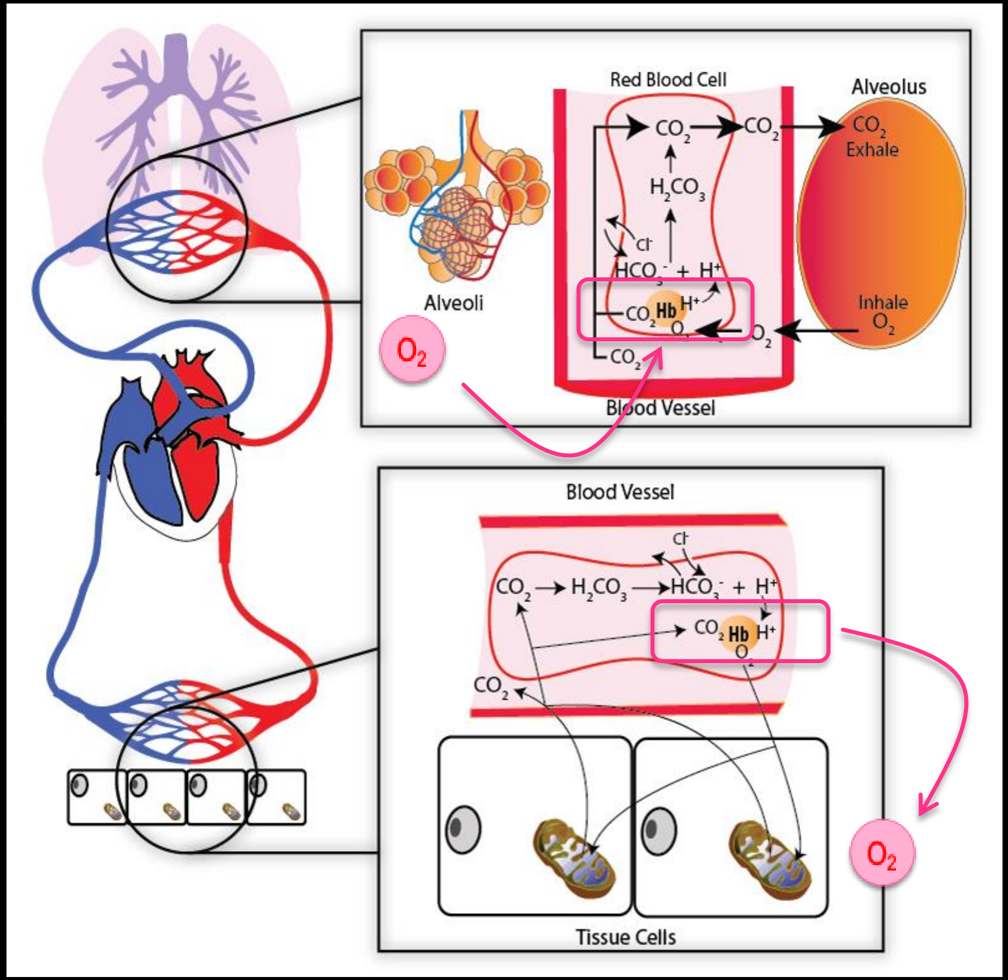
- *Funding*
  - *NIGMS, NHLBI, DoD, DARPA, ARPA-H*
  - *American Heart Association*
  - *Doris Duke Foundation*
  - *Children's Discovery Institute*
  - *Terumo, BCT; Entegrion*
- *Consulting*
  - *Viasys, iNO therapeutics*
  - *Galera Pharmaceuticals*
  - *Nitrox ~ N30Pharma*
  - *Novartis, Biogen*
  - *Etiometry*
  - *Disc Medical*
- *Intellectual Property*
  - *S-nitrosothiol assay systems*
  - *Nanotherapy for Sickle Cell Disease*
  - *ErythroMer artificial RBC system*
- *Equity*
  - *KaloCyte, Inc.; Co-Founder & Chief Scientific Officer*

Elements of Oxygen Delivery System

Each Element Exhibits Homeostatic Control and Integrated Compensation to Stabilize Coupling between O_2 Delivery & Consumption

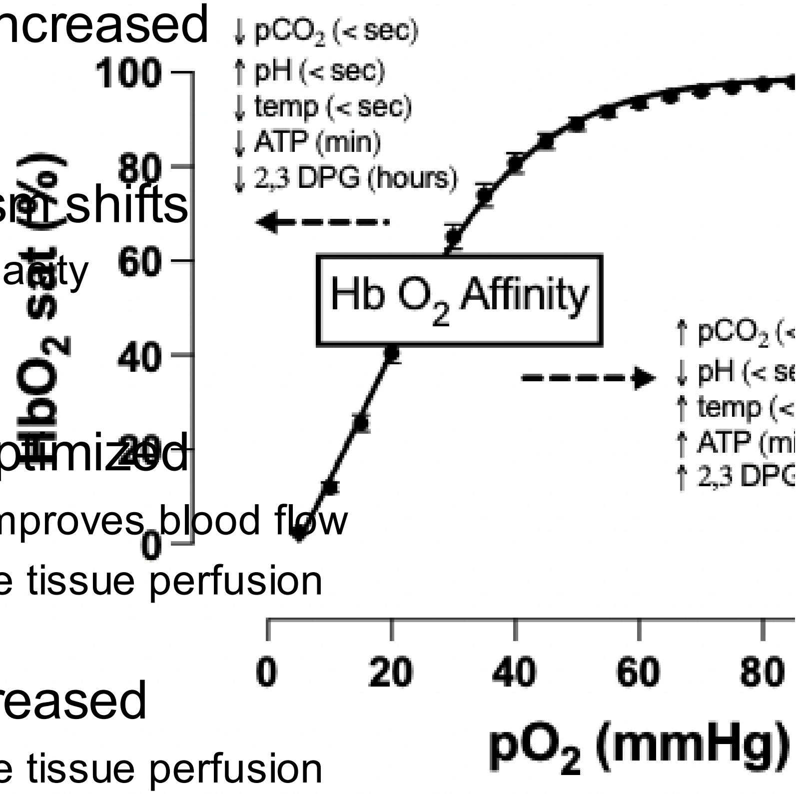


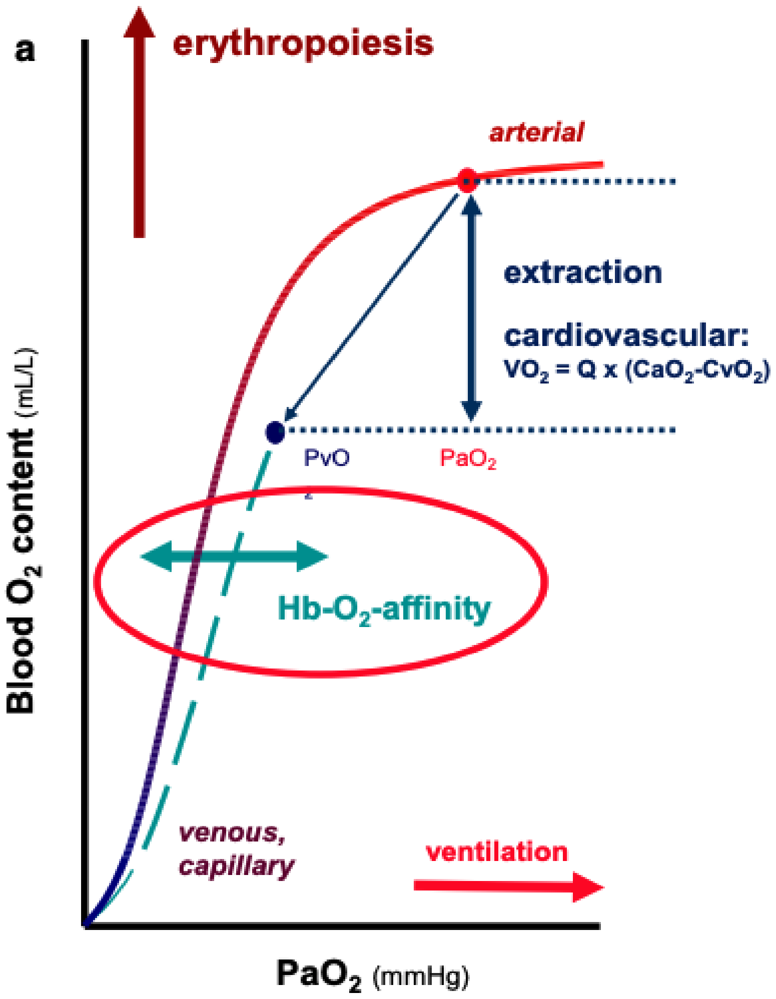


Changes to RBCs are Central to High Altitude Adaptation

time scale is days to weeks

- RBC mass is acutely increased
  - ↑ O_2 carrying capacity
- RBC energy metabolism shifts
  - ↑ antioxidant system capacity
  - ↑ O_2 release efficiency
- RBC vasoregulation optimized
  - ↑ hypoxic vasodilation, improves blood flow
  - ↓ cardiac work to achieve tissue perfusion
- RBC deformability increased
  - ↓ cardiac work to achieve tissue perfusion





Pharmacologic Induction of Tolerance to Hypoxia & Hypothermia
PhIT HyHo

- *Aim 1: Determine ex vivo pharmacodynamics for drug library with known favorable effect upon RBC attributes and PhIT – HyHo potential.*

- *Aim 2: Screen in vivo efficacy of lead candidates (SA1) from the PhIT-HyHo drug library in rodent models of exercise under hypoxia and/or hypothermia.*

Table 2: Pressure, Oxygen & Temperature Levels for Simulation of Extreme Conditions at Altitude

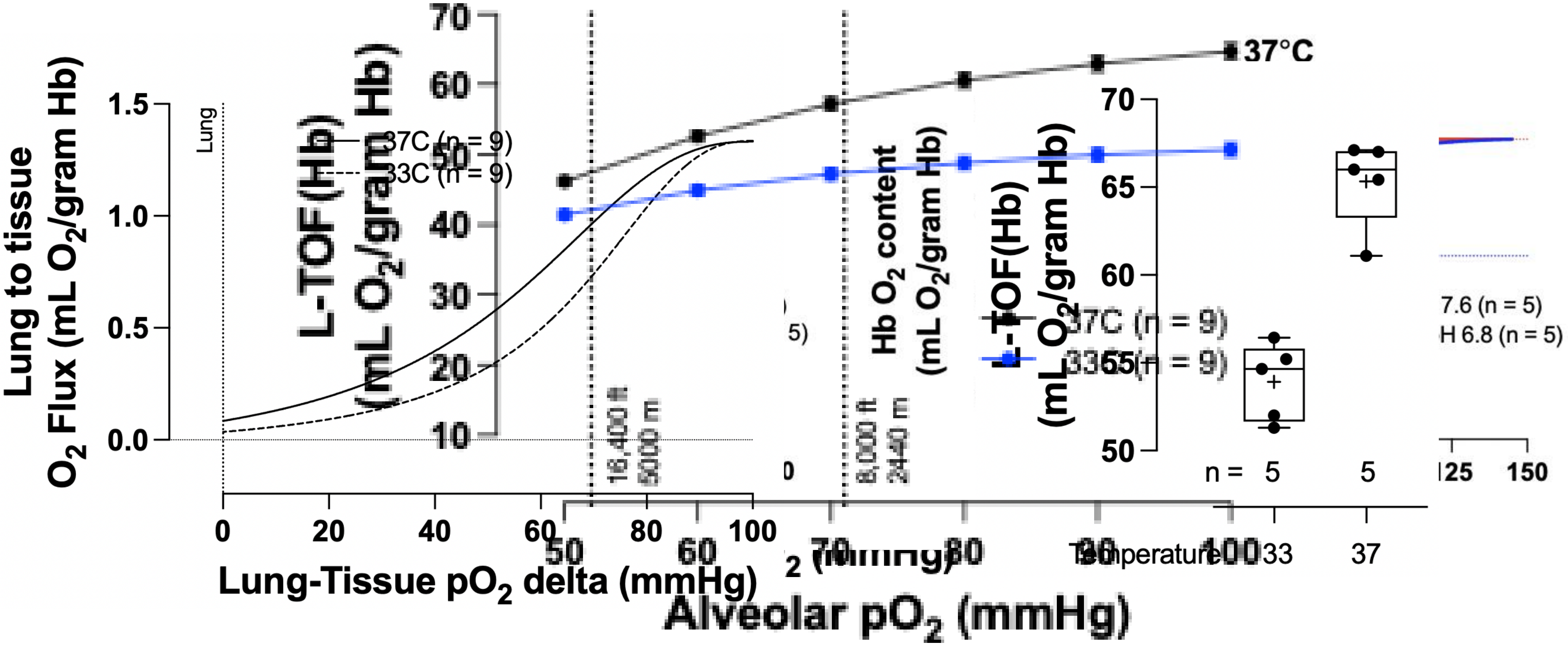
Altitude		Baro Pressure		Oxygen			Ambient Temp		Ref Site
ft	m	mmHg	kPa	FiO_2 %	P_AO_2 Torr	SaO_2%	ºF	ºC	
0	0	760	100	21	100	98	60	15	sea level
8,000	2,438	564	75	15	71	92	30	-1	aircraft cabin
16,400	5,000	405	54	11	52	86	2	-16	Dorah Pass

Table 1 PhIT – HyHo Drug Candidate Library – Anticipated Effects upon RBC function

RBC Attribute Target	Drug	Action - (Anticipated Effect upon RBCs)
Antioxidant & Energetics	metformin[19-24]	AMPK activator/NADH dehydrogenase inhibitor (↑ resilience to oxidative stress)
Biomechanics	imatinib[25,26]	Syk tyrosine kinase inhibitor (↑ deformability - ↑ perfusion)
Vasoregulation & Control of Regional Blood Flow	efaproxiral[27-30]	lowers Hb-O_2 affinity (↑ O_2 release)
	nor-NOHA[31-33]	Arginase inhibitor (↑ vasoactivity – optimized regional blood flow)
	mitapivat[34-37]	PKR activator (↑ vasoactivity - optimized regional blood flow)

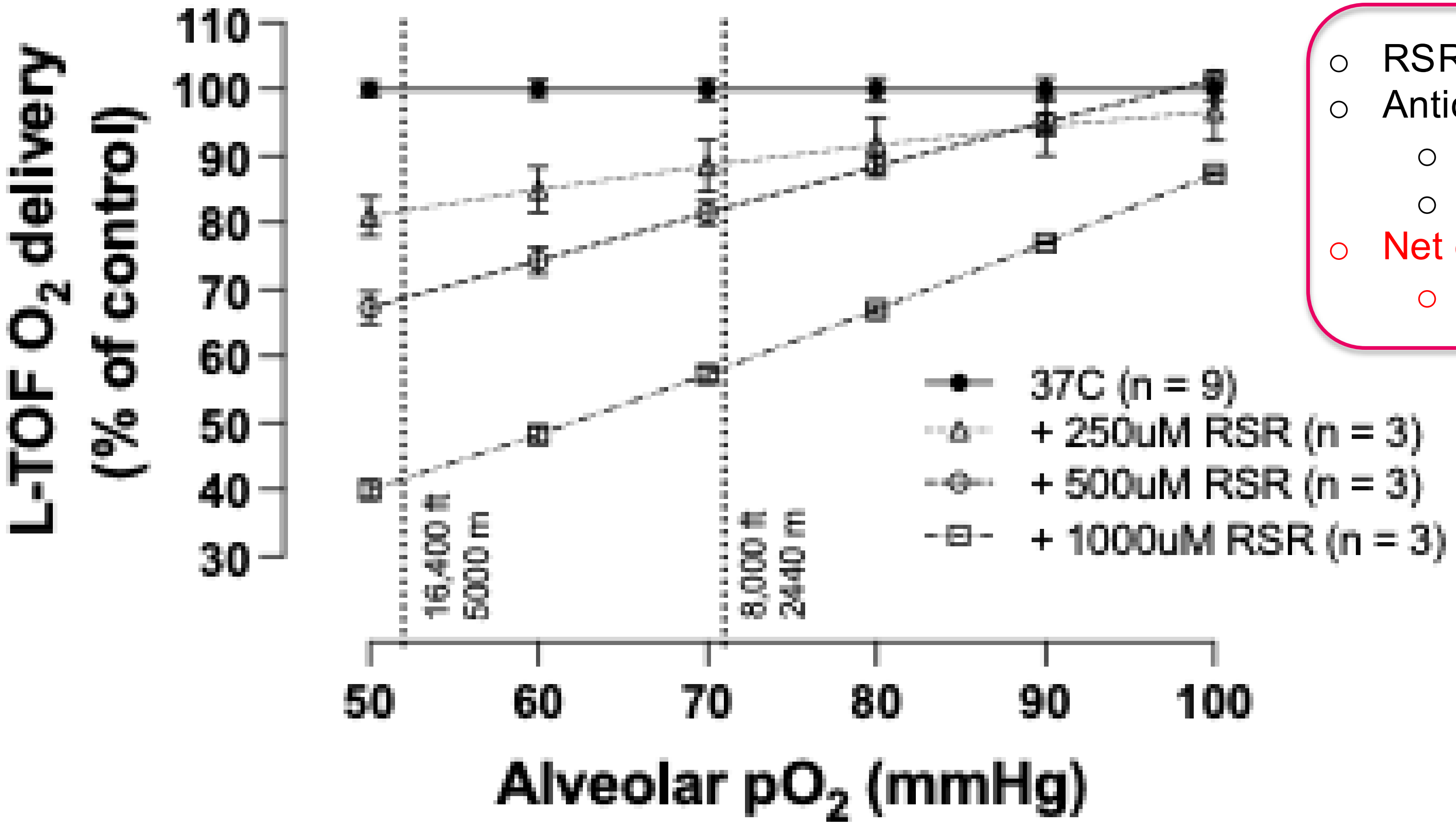
AMPK: adenosine monophosphate-activated protein kinase, GSH: glutathione, NADPH: Nicotinamide adenine dinucleotide phosphate, PKR: pyruvate kinase-R

Assessment of Lung to Tissue (RBC) O_2 Delivery Capacity



RSR 13 (Efaproxiral): Effect on O_2 Delivery Capacity

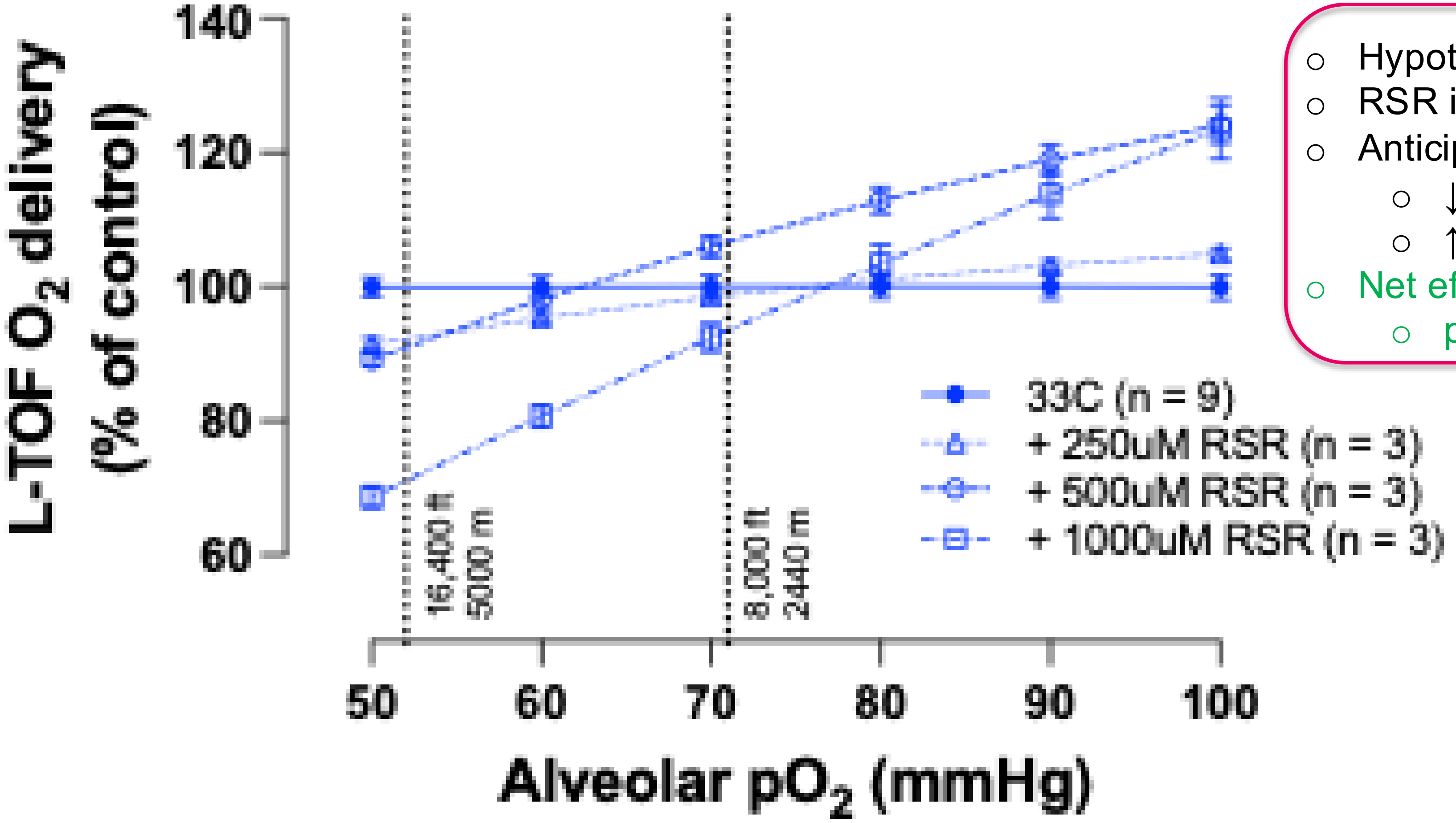
normothermia - with simulated ascent to 5,000m (~ 50% ↓ p_AO_2)



- RSR is "R-shifting": lowers Hb~O_2 affinity
- Anticipated impact:
  - ↓ O_2 capture in lung (↓ $SaHbO_2$%)
  - ↑ O_2 release in tissue (↓ $SvHbO_2$%)
- Net effect:
  - progressive ↓ L-TOF with ascent & dose

RSR 13 (Efaproxiral): Effect on O_2 Delivery Capacity

hypothermia - with simulated ascent to 5,000m (~ 50% ↓ p_AO_2)



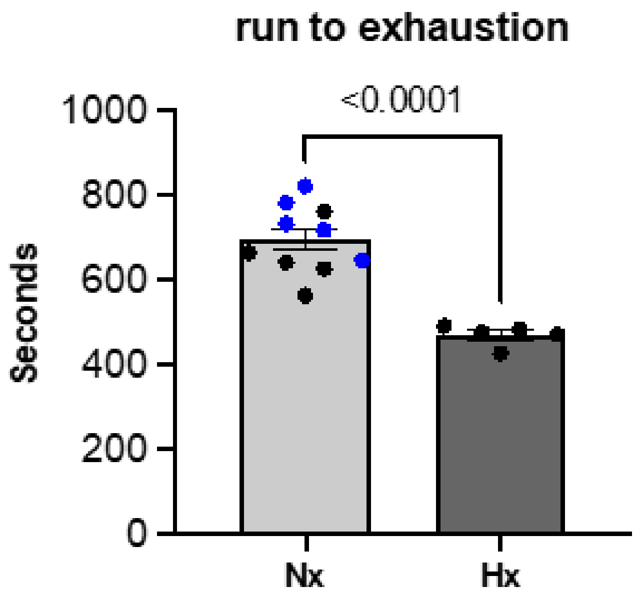
- Hypothermia is "L-shifting": ↑ Hb~O_2 affinity
- RSR is "R-shifting": ↓ Hb~O_2 affinity
- Anticipated impact:
  - ↓ O_2 capture in lung (↓ $SaHbO_2$%)
  - ↑ O_2 release in tissue (↓ $SvHbO_2$%)
- Net effect:
  - progressive ↑ L-TOF with dose / cold

RSR 13 (Efaproxiral): Effect on Exercise Capacity

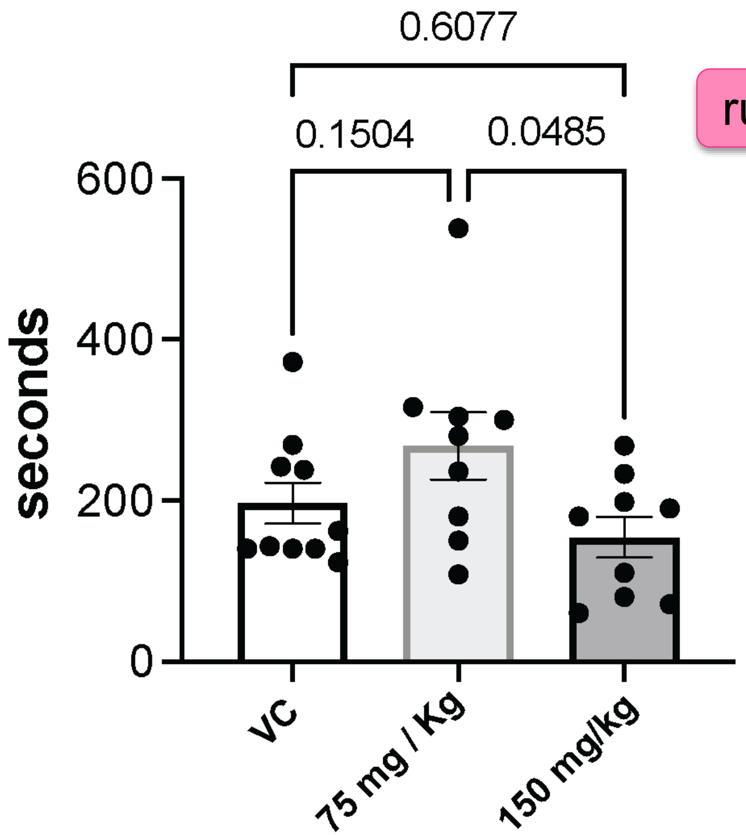
normothermia - with simulated ascent to 5,000m (~ 50% ↓ p_AO_2)

RSR in normothermic hypobaric hypoxia, simulated ascent to 18,000 feet

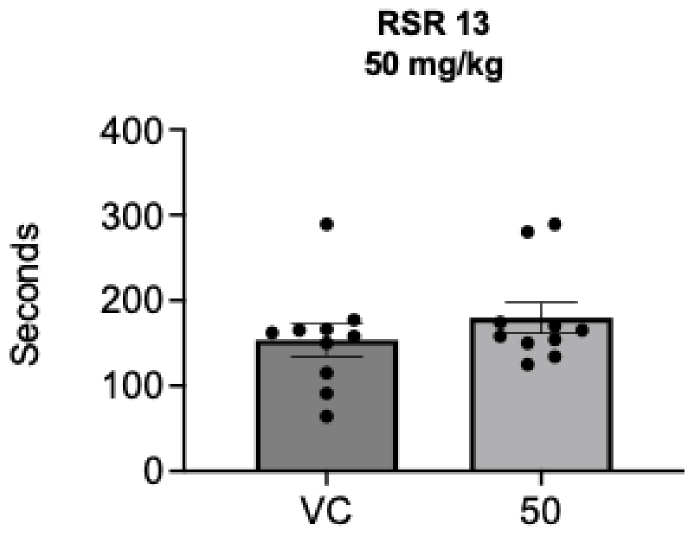
FINDING: modest dose-dependent effect: ~140% improvement @ 75 mg/kg
however, higher dose impairs exercise capacity



Controls +/-
simulated ascent to 18,000 ft



run to exhaustion



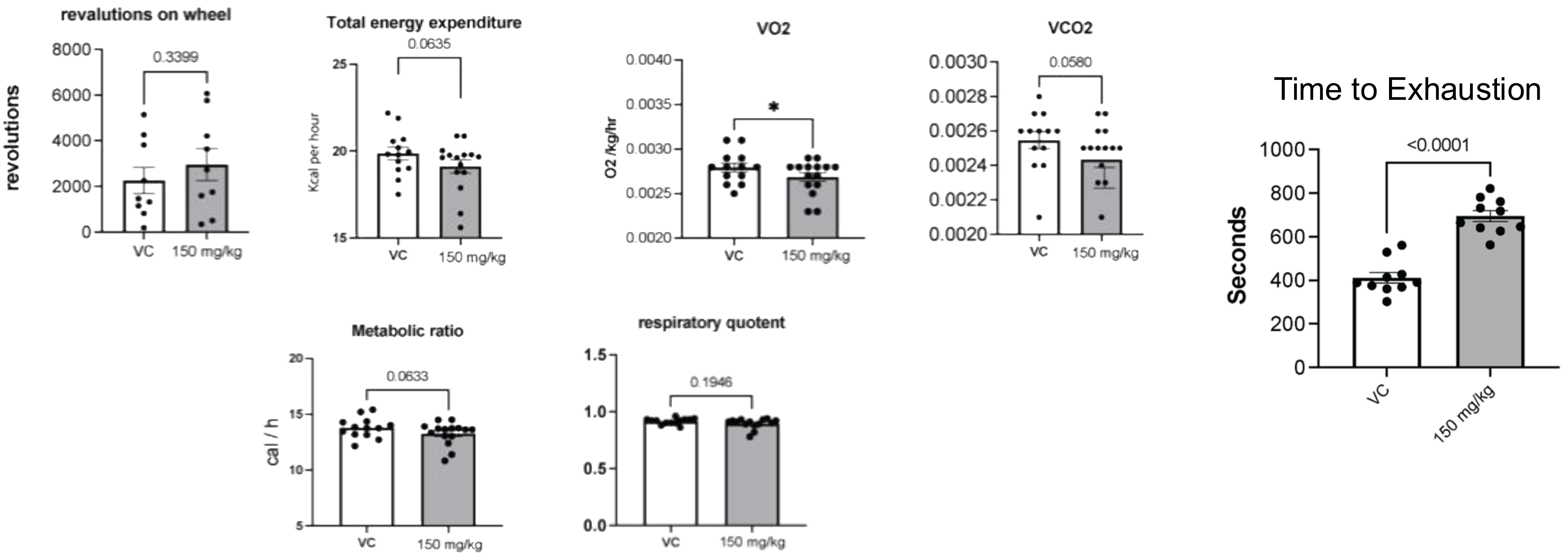
RSR 13 (Efaproxiral): Effect on Exercise Capacity

murine exercise tolerance during cold stress without simulated ascent

RSR in cold stress cold stress (4℃ x 4h) @ Denver (5,280ft /1,609m), ↓ pAO2 ~ 80% rel to Sea Level

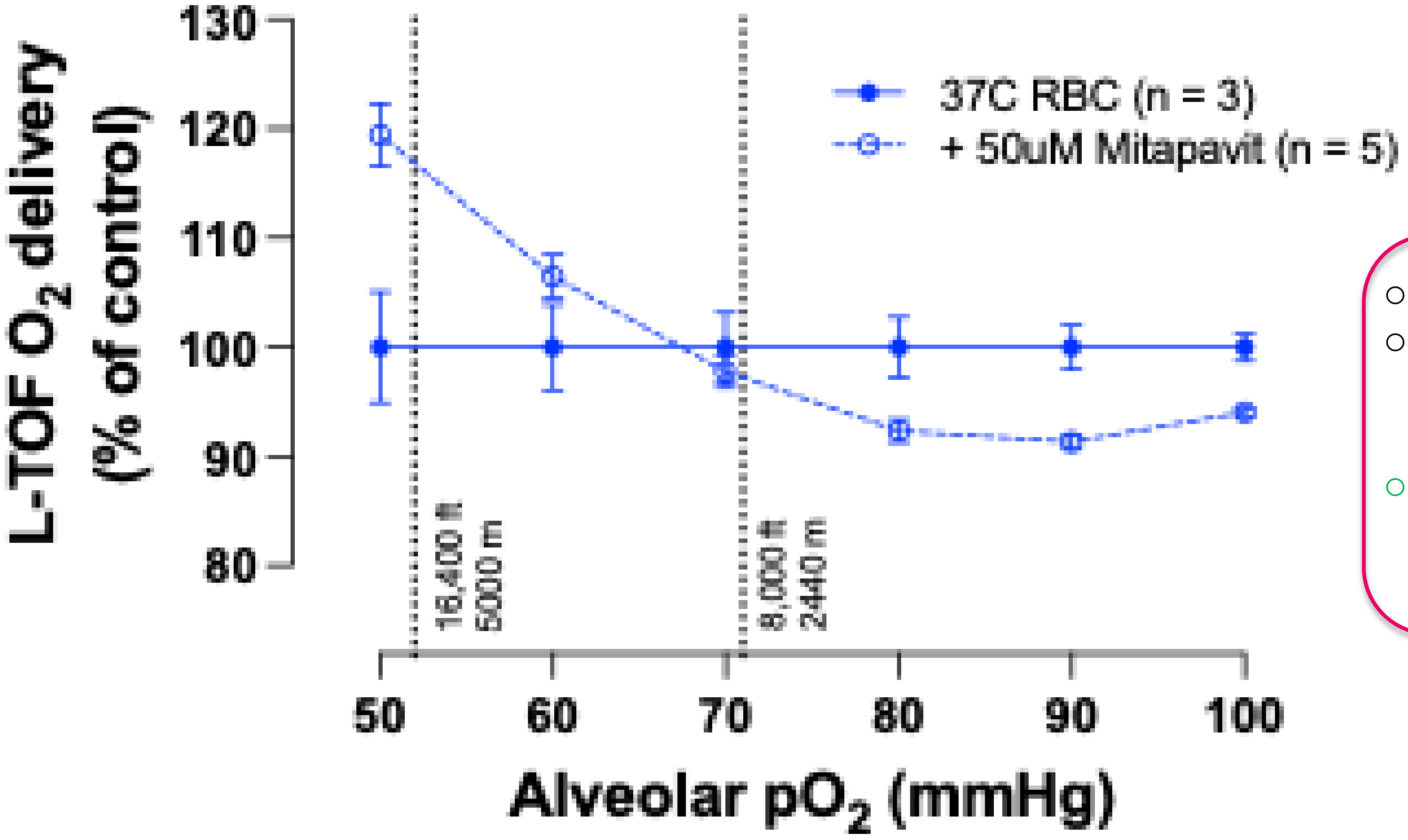
FINDING: ~200% ↑ in exercise capacity (time to exhaustion)

↓ EE, VO_2 indicates ↑ O_2 transport/consumption efficiency



Mitapivat: Effect on O_2 Delivery Capacity

normothermia - with simulated ascent to 5,000m (~ 50% ↓ p_AO_2)



- Mitapivat is "L-shifting": ↑ Hb~O_2 affinity
- Anticipated impact:
  - ↑ O_2 capture in lung (↑ $SaHbO_2$%)
  - ↓ O_2 release in tissue (↑ $SvHbO_2$%)
- Net effect:
  - Modestly Impaired L-TOF < 2,440 m
  - progressive ↑ L-TOF > 2,440 m

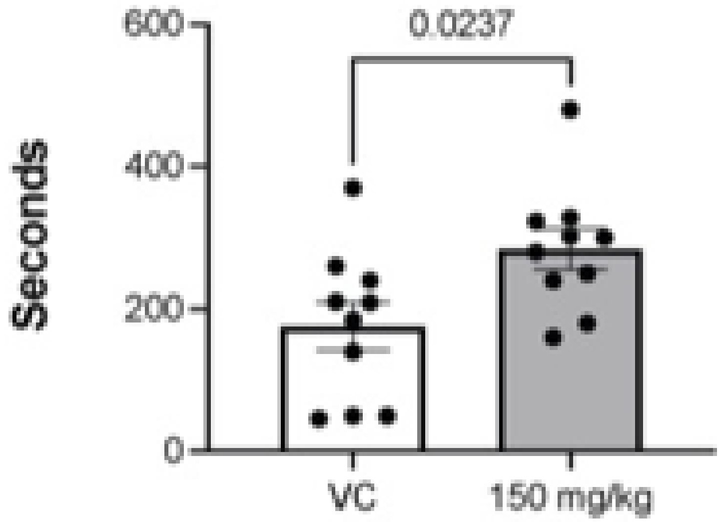
Mitapivat: Effect on O_2 Exercise Capacity

normothermia - with simulated ascent to 5,000m (~ 50% ↓ p_AO_2)

Mitapivat in normothermic hypobaric hypoxia, simulated ascent to 18,000 feet

FINDING: significant (~ 175%) improvement in time to exhaustion

run to exhaustion



Pharmacologic Induction of Tolerance to Hypoxia & Hypothermia
Use Cases

- *Improve O_2 Delivery in Warfighters Operating in Extreme Environments*
  - *Cold Stress – Hypothermia (proof of concept demonstrated for exercise capacity, expect benefit for cognitive)*
  - *Hypobaric Hypoxia – Altitude (proof of concept demonstrated)*
  - *Heat Stress (not yet tested)*

- *Improve O_2 Delivery in Casualties Suffering Extreme Physiologic Stress*
  - *Hemorrhagic Shock (improve anemia tolerance, improve stored blood quality)*
  - *Respiratory Failure (analogous to hypobaric hypoxia)*
  - *Low Cardiac Output (O_2 delivery limited by blood flow, rather than O_2 content)*

Pharmacologic Induction of Tolerance to Hypoxia & Hypothermia
Potential Path Forward (Use Case #1: Warfighter Performance)

- *Aim 1: Identify new candidates for PhIT HyHo activity*
  - *Continue current in vitro platform, add cognitive performance to in vivo model of exercise capacity*
  - *Objective: Identify candidates with superior efficacy and pharmacokinetic features (duration of action, etc.)*

- *Aim 2: Test current PhIT HyHo candidates for efficacy in humans*
  - *Exercise Capacity in cold stress and hypobaric hypoxia (alone and in combination)*
  - *Cognitive Performance (+/- exercise) in cold stress and hypobaric hypoxia (alone and in combination)*
  - *Evaluate drug delivery route and dosing (oral or patch)*
  - *Objective: Establish efficacy (> 25% sustained increase in exercise capacity and task performance)*

Pharmacologic Induction of Tolerance to Hypoxia & Hypothermia
Potential Path Forward (Use Case #2: Casualty Care)

- *Aim 1: Evaluate Efficacy of PhIT HyHo Candidates for Hemorrhagic Shock*
  - *Define improvement in anemia tolerance (after treating animal following hemorrhage/resuscitation (non-blood) with PhIT HyHo Candidate)*
  - *Define improvement in transfusion efficacy (after treating blood units with PhIT HyHo Candidate)*
- *Aim 2: Evaluate Efficacy of PhIT HyHo Candidates for Respiratory Failure*
  - *Define improvement in oxygenation following lung injury (unintubated, without supplemental oxygen)*
- *Aim 3: Evaluate Efficacy of PhIT HyHo Candidates for Low Cardiac Output*
  - *Define improvement in tissue oxygen delivery in shock models (hemorrhage/resuscitation, myocardial injury)*

Grateful Acknowledgment

- ## University of Maryland

  Center for Blood Oxygen Transport & Hemostasis

  Doctor Lab
  Stephen Rogers, PhD
  Zoreh Safari, PhD
  Antonio Rinaldo, PhD
  Sambhu Pillai, DVM
  Regina Adao, PhD
  Julie Proctor, MS
  Mary Brummet, MS
  Karen Nichols, MS
  Daniel Bennett, MS
  Lamia Tithy, PhD (candidate)
  Mia Alexander, BS
  Riley Himmelberger, BS

  Funding: NIGMS, NHLBI, NICHD, DoD, DARPA, ARPA-H, AHA, Doris Duke Foundation, Children's Discovery Institute

- ## University of Colorado

  RBC Metabolomics & Proteomics
  Angelo D'Alessandro, PhD   Julie Haines, PhD
  Monika Dzieciatkwowska, PhD   Travis Nemkov, PhD

  Murine Exercise Physiology & High Altitude Physiology
  Dave Irwin, PhD   Charistina Lisk, PhD

- ## Air Force Research Laboratory

  711th Human Performance Wing / En Route Care Section
  Jody Cantu, PhD