Preconditioning is Hormesis

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HORMESIS CONCEPT

- Low doses of numerous stressors (e.g. exercising, intermittent fasting, hypoxia, heat, cold, ionizing/non-ionizing radiation, electricity, toxins, chemicals/drugs) can stimulate a wide range of adaptive responses.

- These induced adaptive responses have the potential to profoundly affect the success of medical interventions for numerous disorders (e.g., heart attack, stroke, shock, brain traumatic damage, organ transplant, surgeries).

- Stressors that trigger adaptive responses also offer ways to enhance healthy aging, improve human performance and prevent damage to tissues exposed later to injurious levels of stressors and enhance tissue repair.

- At the center of this adaptive response concept is the phenomenon of hormesis, a biphasic dose response that mediates processes by which human adaptation and performance may be improved, optimizing the dosimetry while providing the underlying molecular mechanism.

- What is hormesis, how can it be used to achieve these public health and medical advances?

HORMESIS

Definition:

- Dose response phenomenon characterized by a low dose stimulation and a high dose inhibition.

- It is a non-monotonic/biphasic dose response, with specific dose response features.

EVIDENCE OF HORMESIS

General Summary:

- Hormesis databases: many thousands of dose responses indicative of hormesis using rigorous entry/evaluative criteria.

EVIDENCE OF HORMESIS

General Summary:

- Hormesis is a very general phenomenon: independent of model (e.g. plant, microbial, invertebrate, vertebrate, human) (e.g. in vitro/in vivo), endpoint, agent and level of biological organization (i.e. cell, organ, individual).

- Generally similar quantitative features with respect to amplitude and range of the stimulatory response.

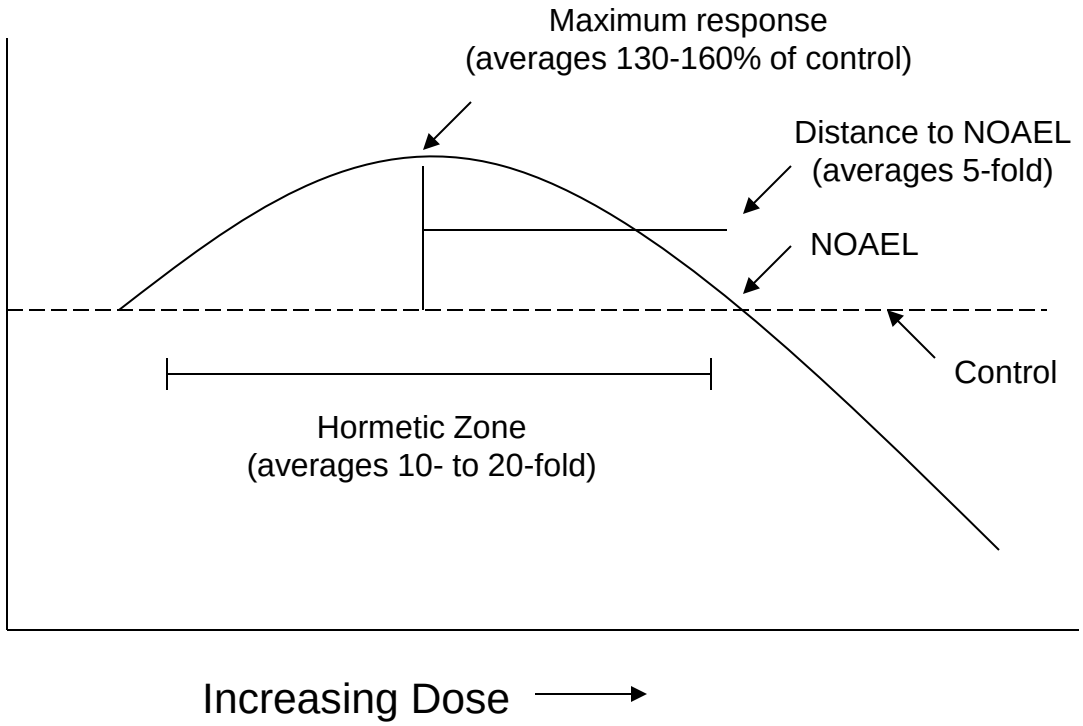
DOSE RESPONSE

Stimulation Amplitude:

- Modest, 30-60% > Control
- Usually Not More Than 100% > Control

Stimulation Range:

- Typically over a 5 to 20-fold Range Immediately Below Threshold



Dose-response curve depicting the quantitative features of hormesis

- Hormetic responses are integrative responses across multiple levels of biological organization;

- Cell proliferation
- Fecundity
- Tissue Repair
- Behavioral/Learning
- Disease/Injury Resistance/Pre- Post-Conditioning
- DNA Damage/Tumor Incidence
- Aging/Longevity

WHAT IS HORMESIS INDICATING?

- The low dose stimulation is different than the high dose inhibition/toxicity;
- Low dose stimulation: It is a measure of biological performance, not toxicity;
- It determines how much a system can respond.

KEY OBSERVATIONS

- Hormesis is the first quantitative estimate of biological plasticity.

- The Hormesis stimulatory response is constrained by the limits of plasticity.

HORMETIC MECHANISMS

- Many studies provide mechanisms to account for hormetic responses;
- Each mechanism is unique to the model, tissue, endpoint and agent;
- Regardless of mechanism the quantitative features of the dose response are similar.

PRE- POST-CONDITIONING HORMESIS

Concepts:

- When sufficient doses are used preconditioning dose responses are biphasic and conform to the quantitative features of the hormetic dose response.
  - Evidence – several hundred examples in the published literature

PRE- POST-CONDITIONING HORMESIS

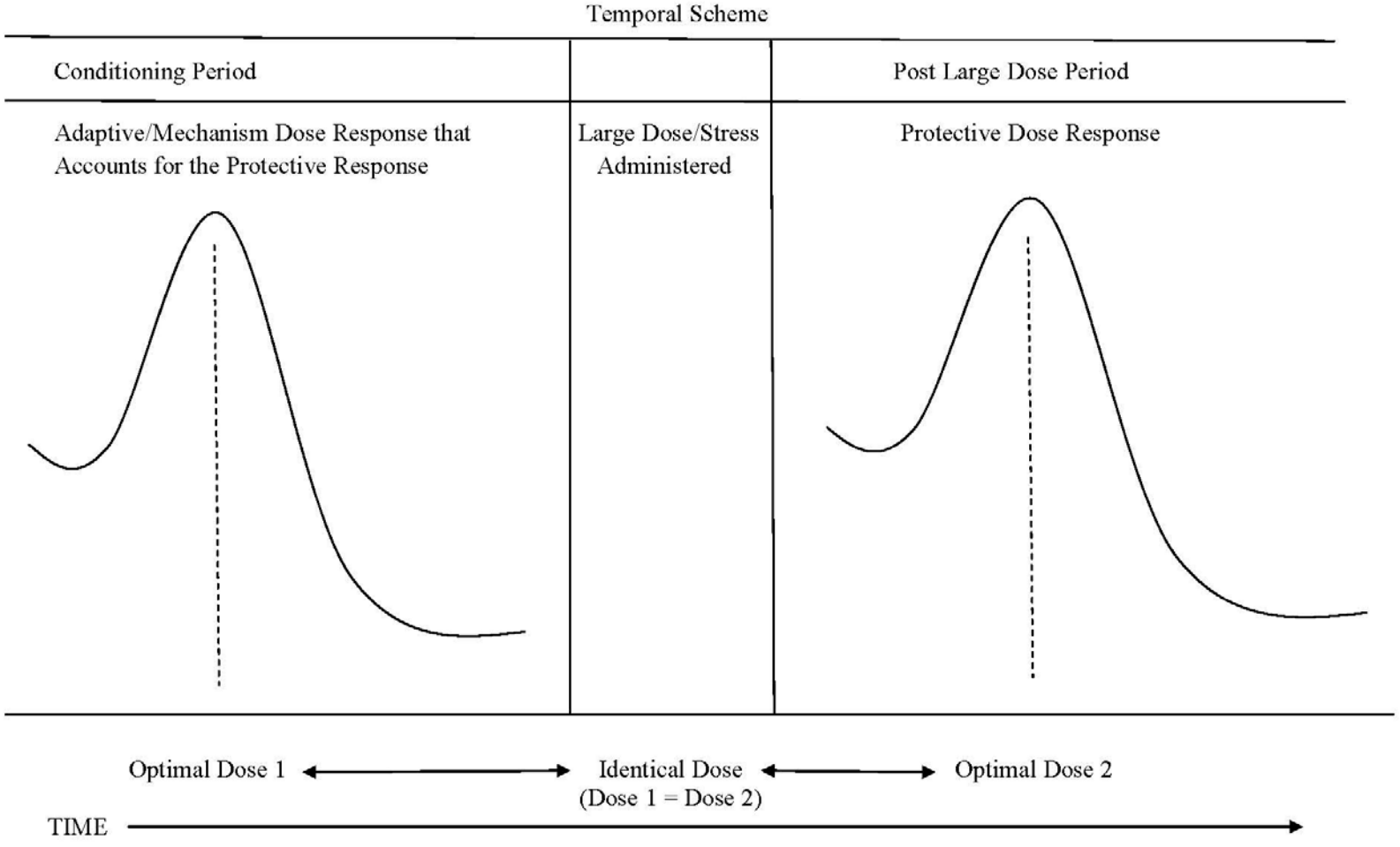
Concepts:

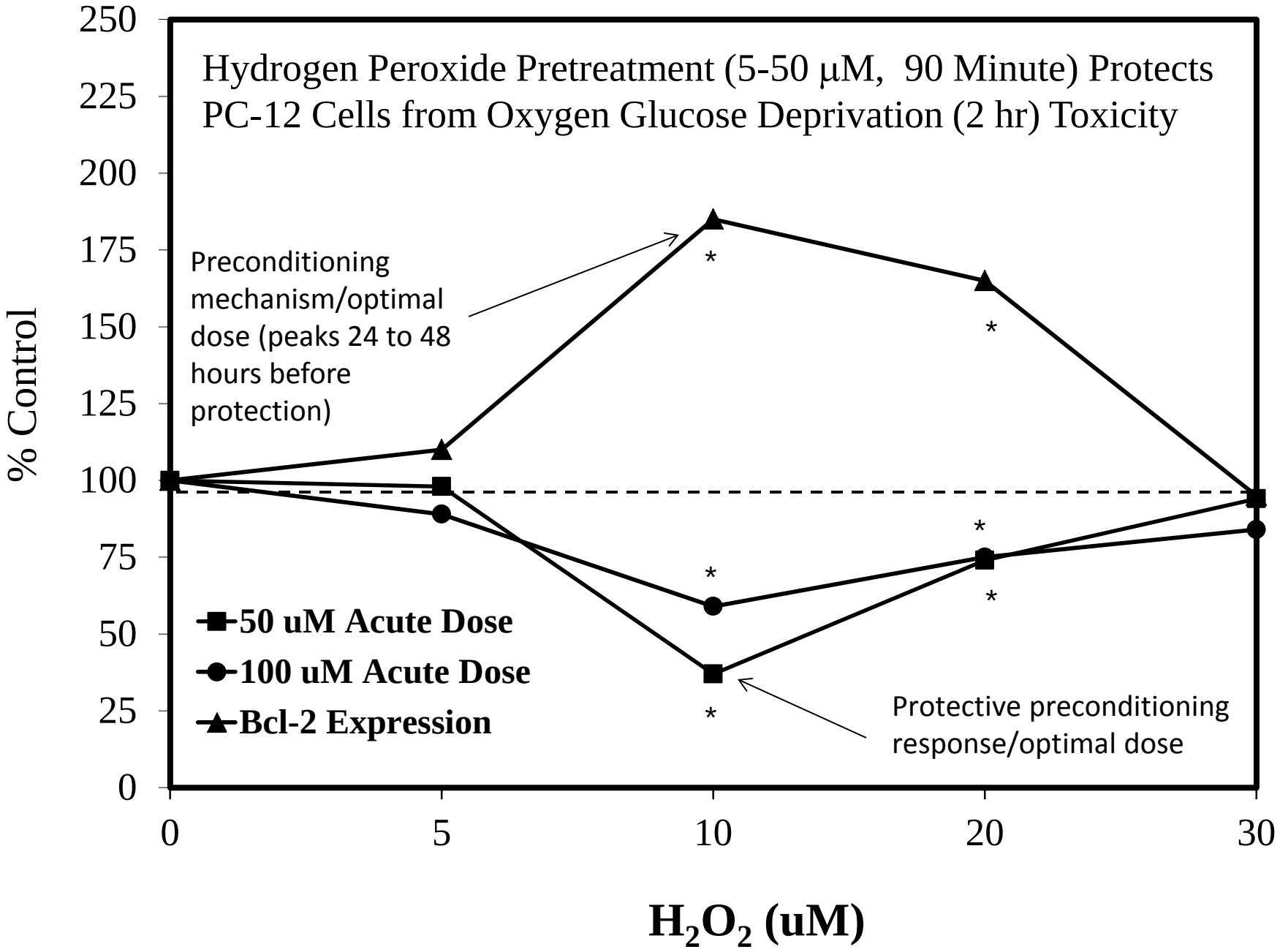
- The hormetic dose response for pre- post-conditioning is independent of:
  - Biological model
  - Organ
  - Cell type
  - Inducing agent
  - Endpoint
  - Mechanism

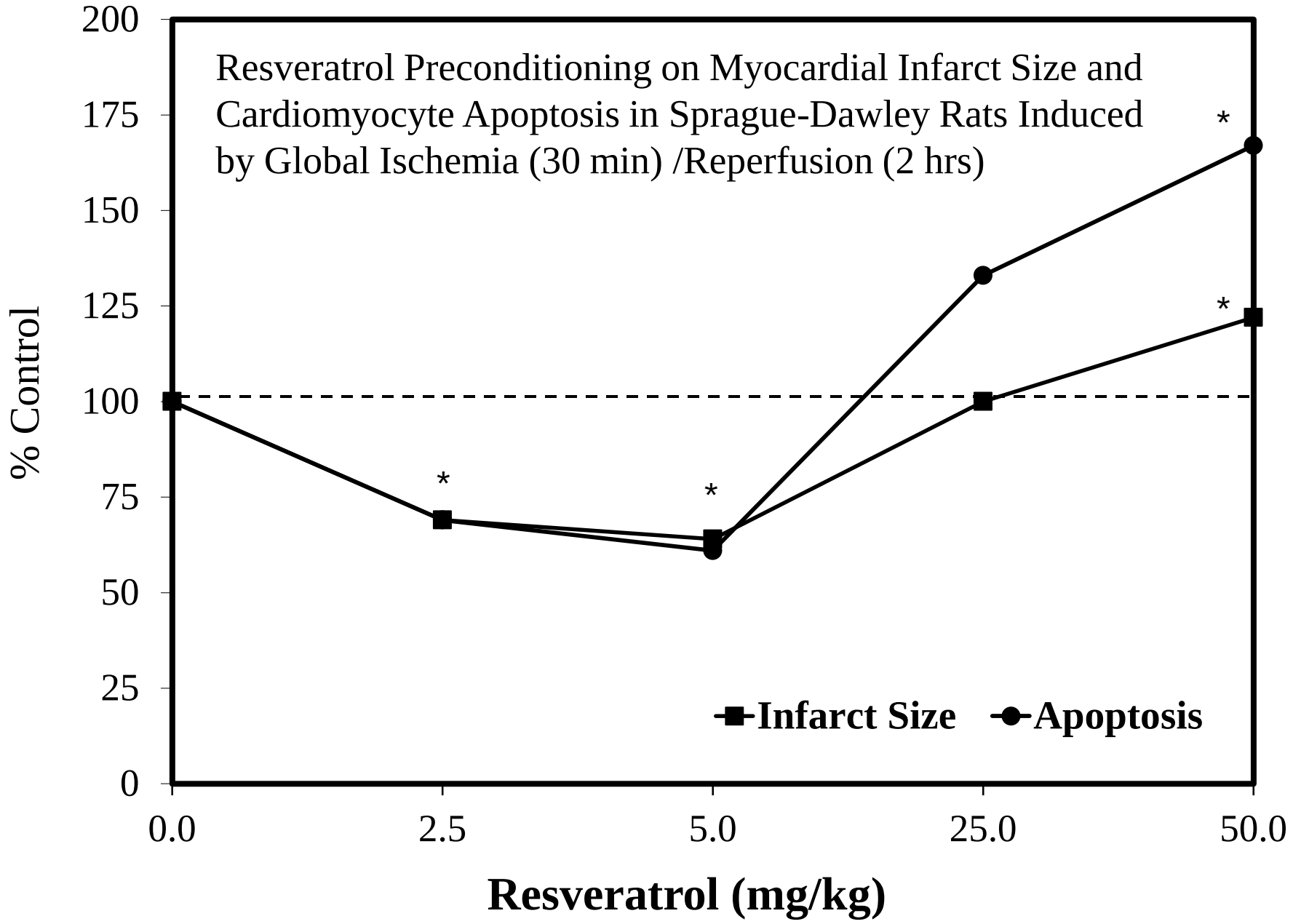
PRE- POST-CONDITIONING HORMESIS

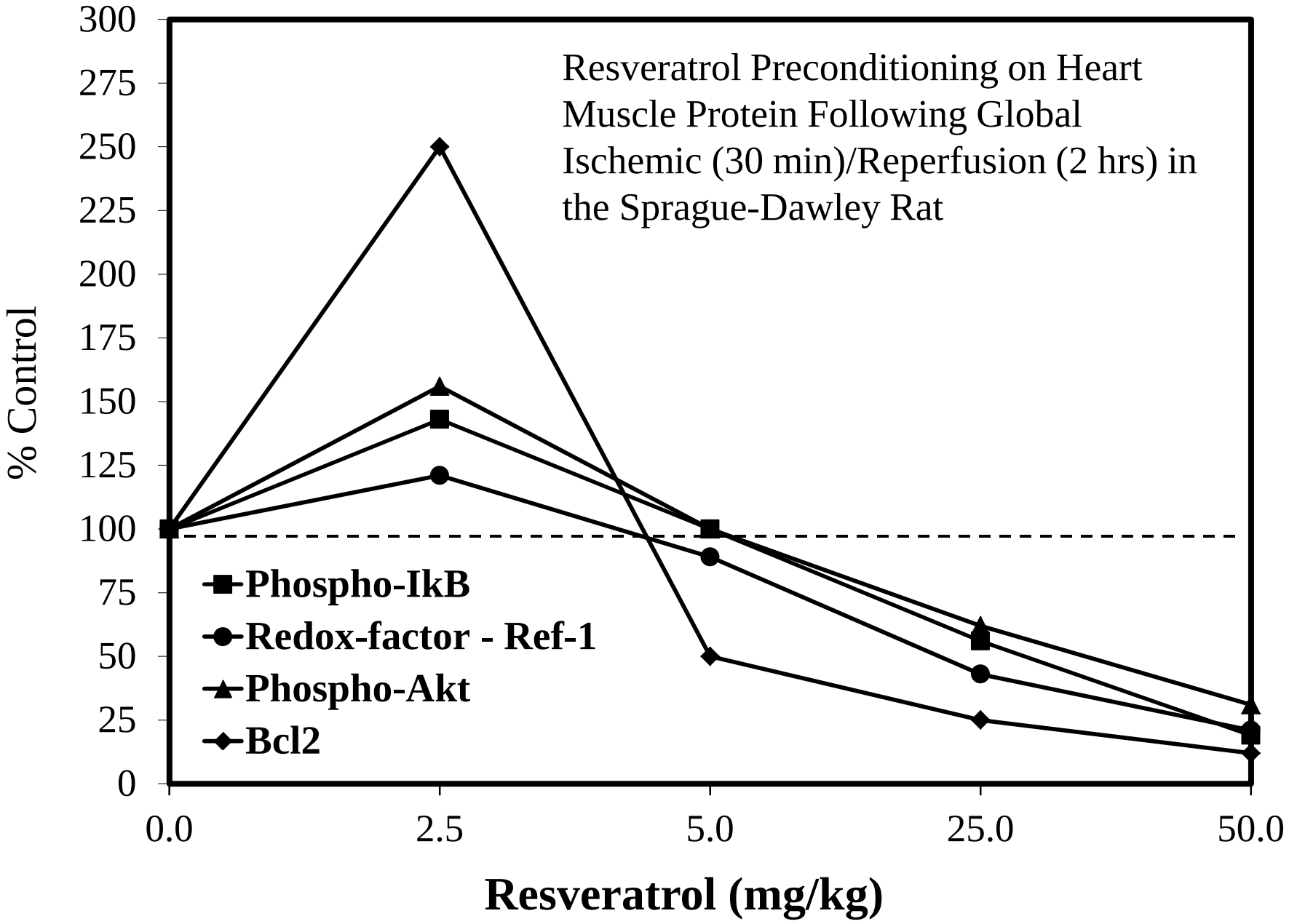
Integrating dose, temporal and mechanistic relationships between the conditioning dose and the protective effects of preconditioning experiments

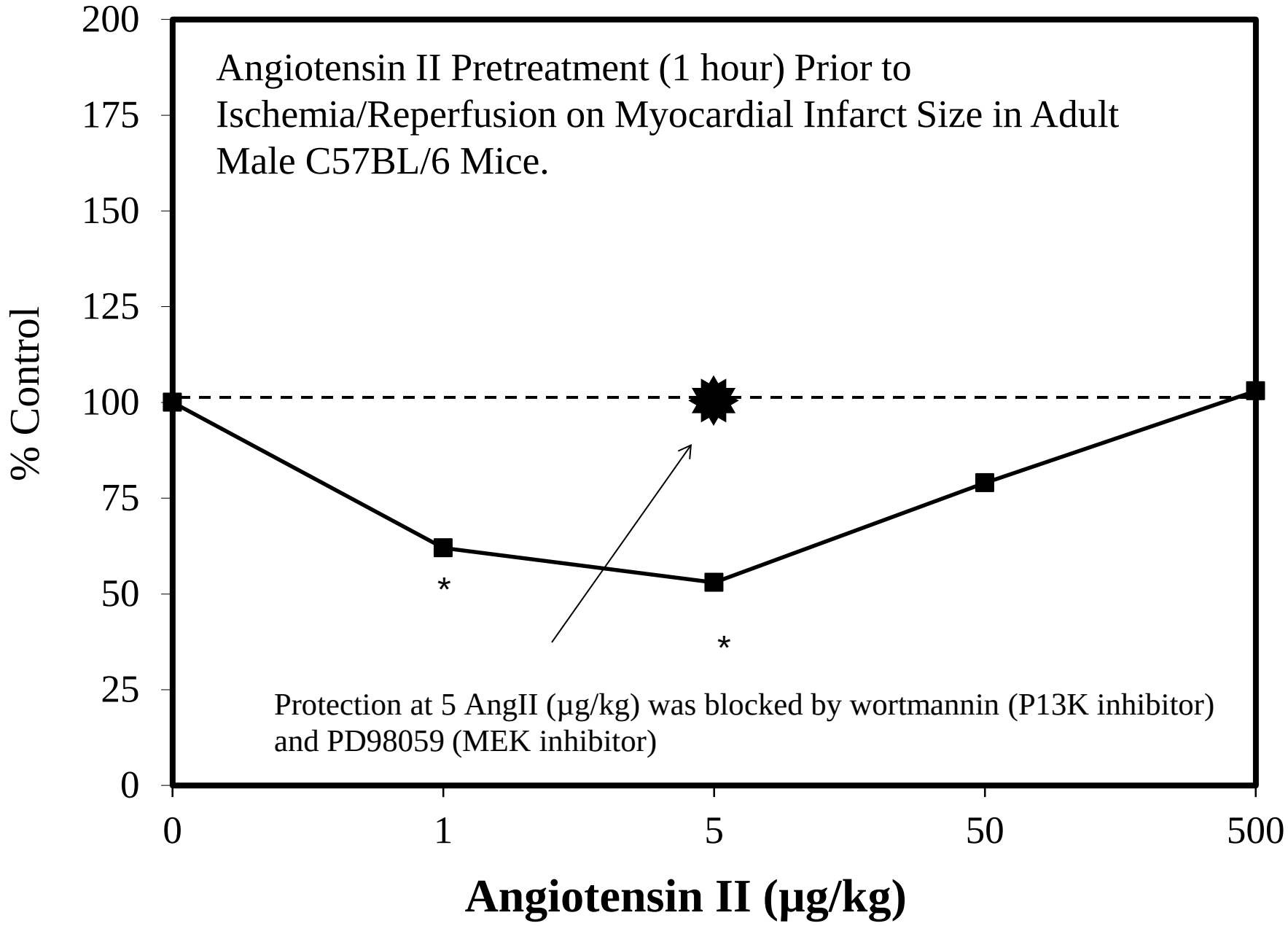
Figure 1. General Preconditioning Scheme: Temporal and Dose-Response Relationship Between Conditioning Dose/Response and Protective Response

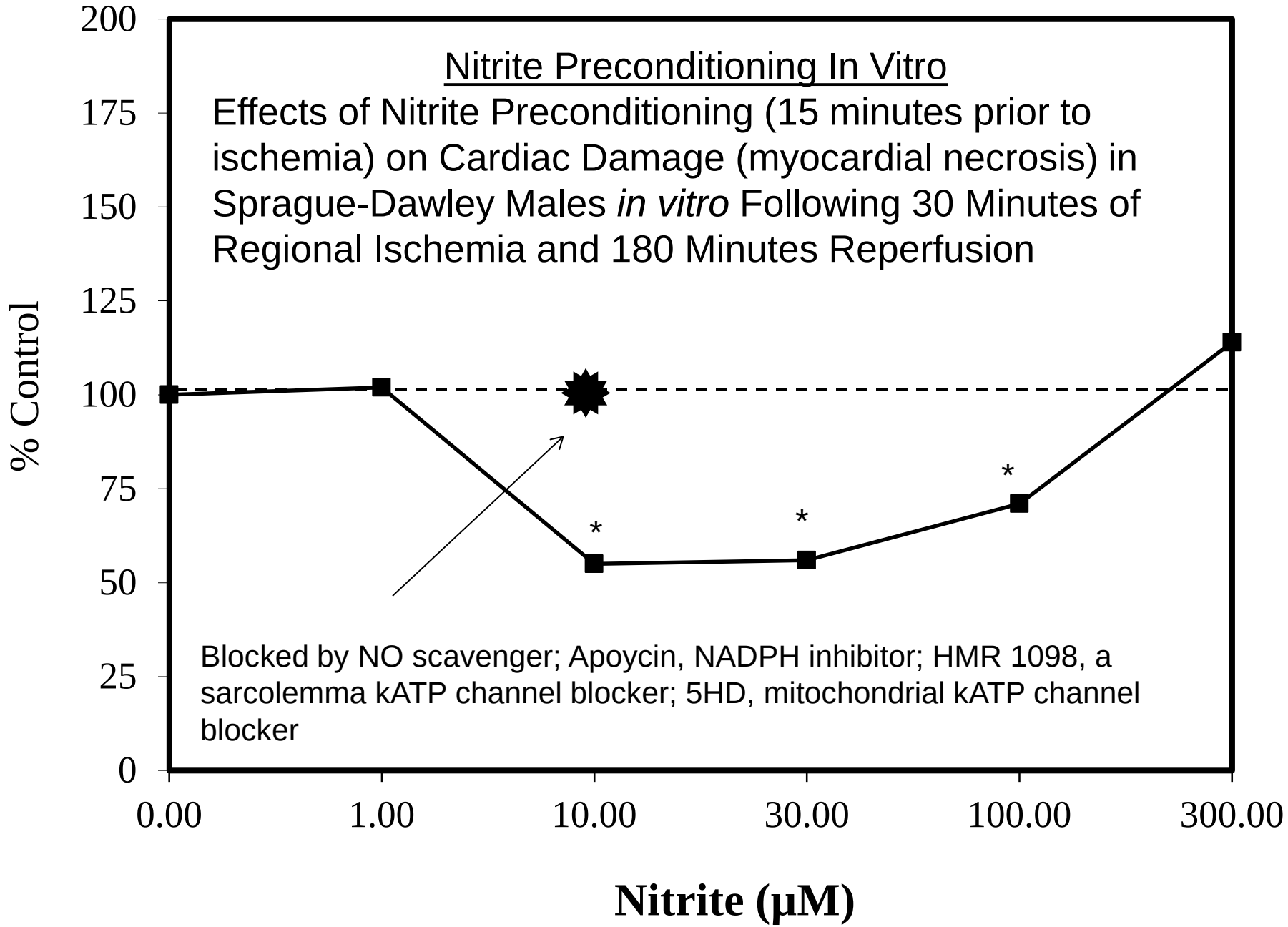


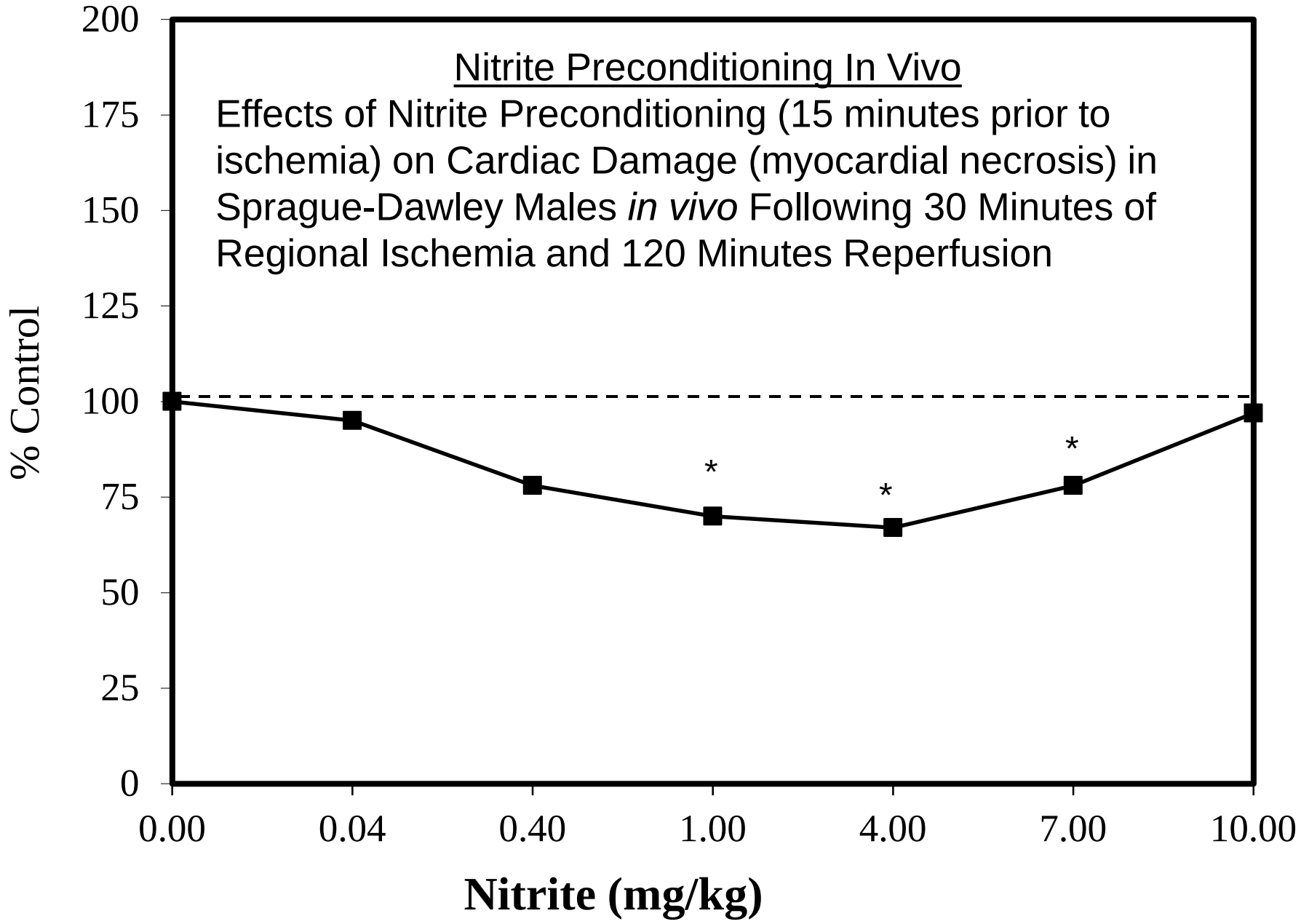

Hydrogen Peroxide Pretreatment (5-50 μM, 90 Minute) Protects PC-12 Cells from Oxygen Glucose Deprivation (2 hr) Toxicity
% Control
250
225
200
175
150
125
100
75
50
25
0
0
5
10
20
30
H2O2 (uM)
Preconditioning mechanism/optimal dose (peaks 24 to 48 hours before protection)
Protective preconditioning response/optimal dose
50 uM Acute Dose
100 uM Acute Dose
Bcl-2 Expression
*

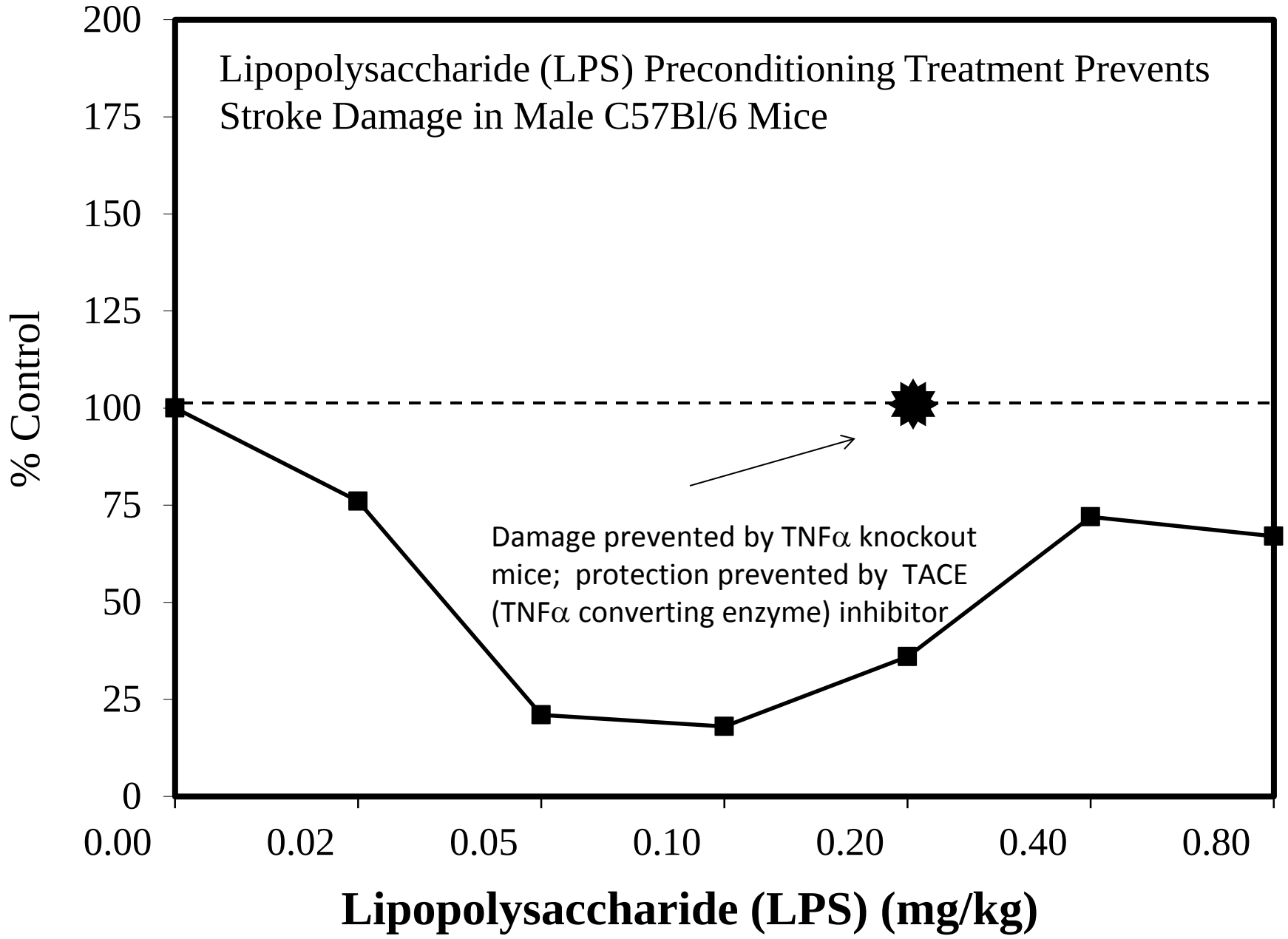

Resveratrol Preconditioning on Myocardial Infarct Size and Cardiomyocyte Apoptosis in Sprague-Dawley Rats Induced by Global Ischemia (30 min) /Reperfusion (2 hrs)
% Control
200
175
150
125
100
75
50
25
0
0.0
2.5
5.0
25.0
50.0
Resveratrol (mg/kg)
Infarct Size
Apoptosis
*
*
*
*

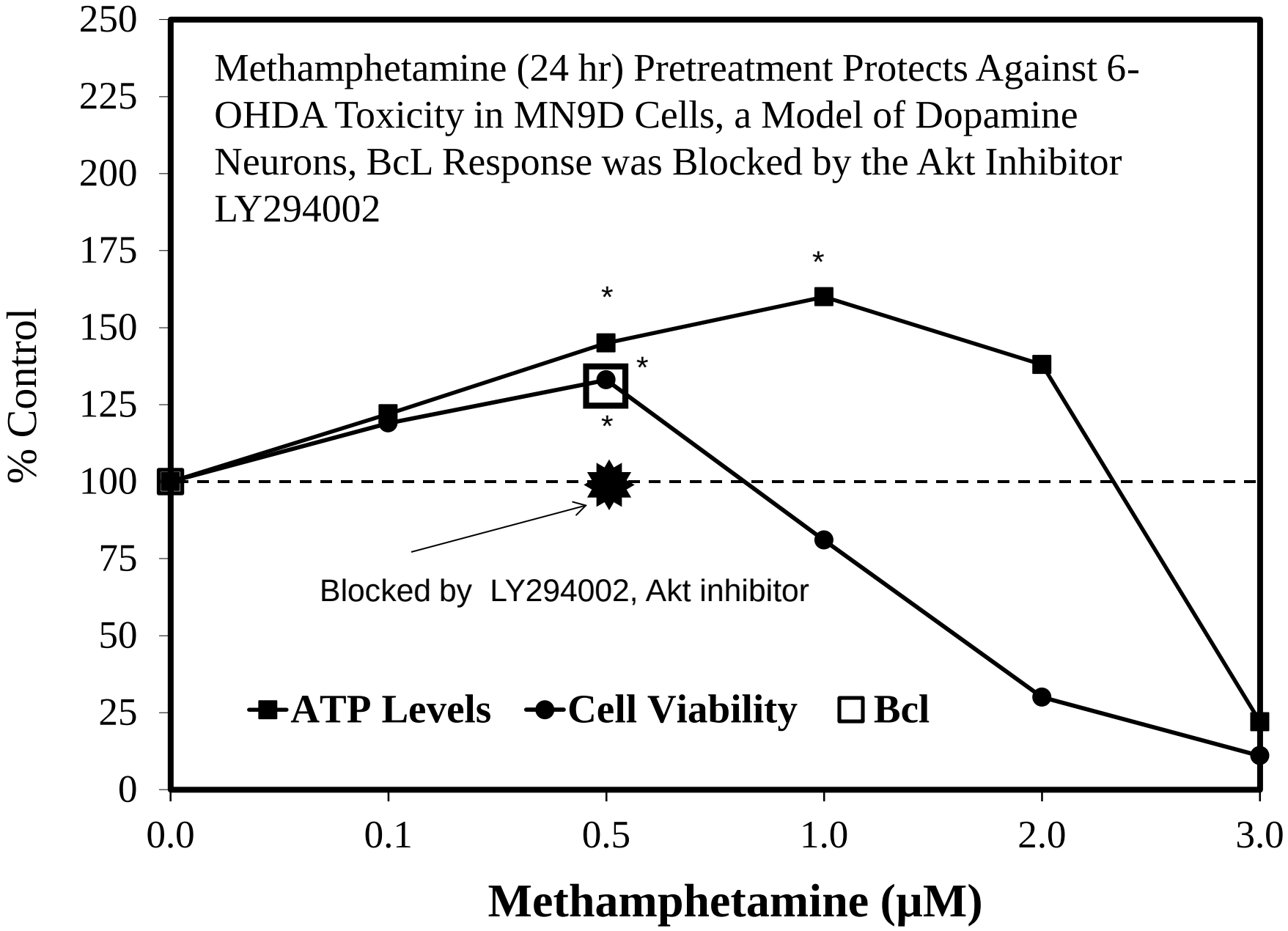

Resveratrol Preconditioning on Heart Muscle Protein Following Global Ischemic (30 min)/Reperfusion (2 hrs) in the Sprague-Dawley Rat
% Control
300
275
250
225
200
175
150
125
100
75
50
25
0
0.0
2.5
5.0
25.0
50.0
Resveratrol (mg/kg)
Phospho-IkB
Redox-factor - Ref-1
Phospho-Akt
Bcl2

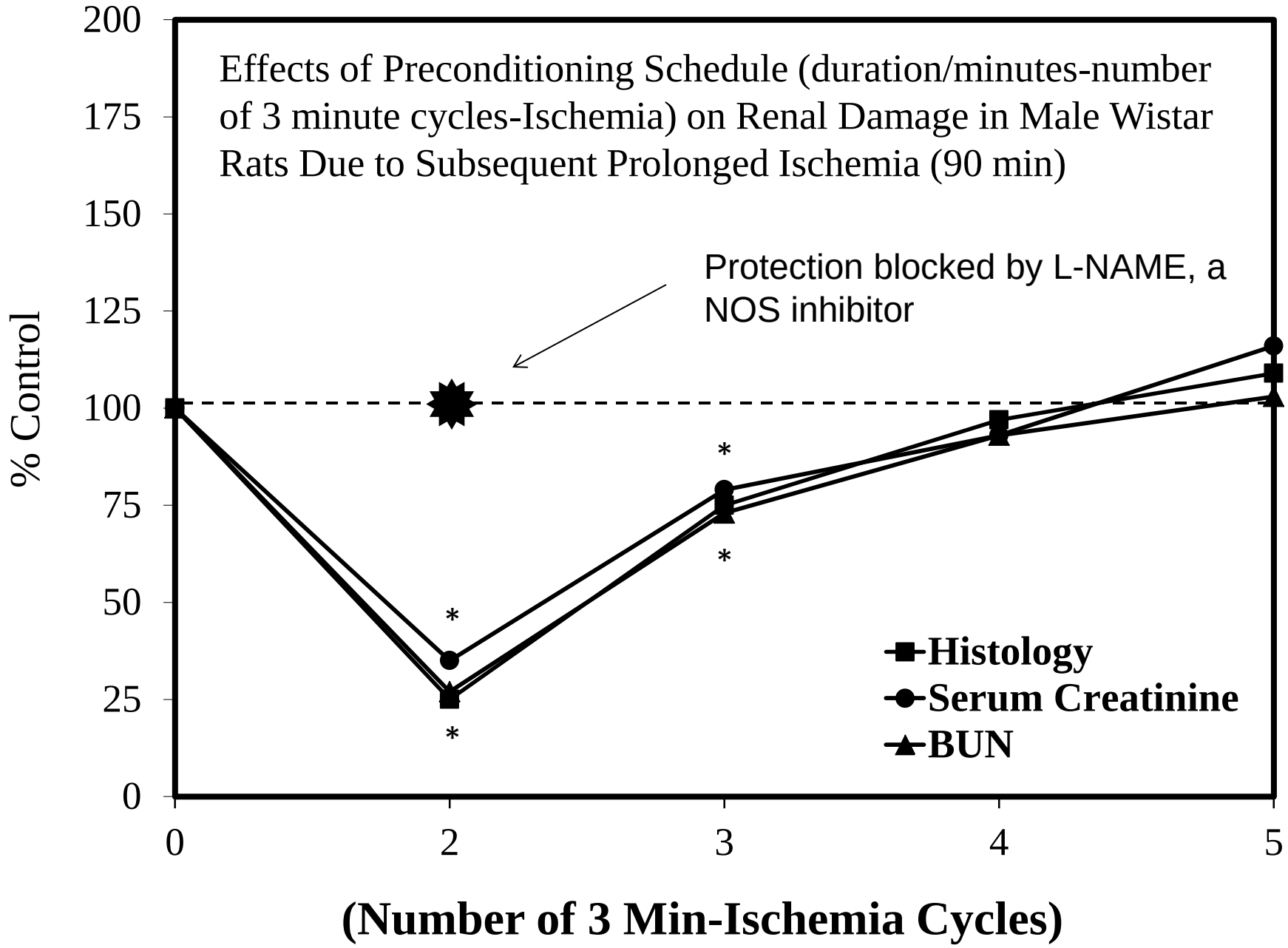

Angiotensin II Pretreatment (1 hour) Prior to Ischemia/Reperfusion on Myocardial Infarct Size in Adult Male C57BL/6 Mice.
% Control
200
175
150
125
100
75
50
25
0
*
*
Protection at 5 AngII (µg/kg) was blocked by wortmannin (P13K inhibitor) and PD98059 (MEK inhibitor)
0
1
5
50
500
Angiotensin II (µg/kg)

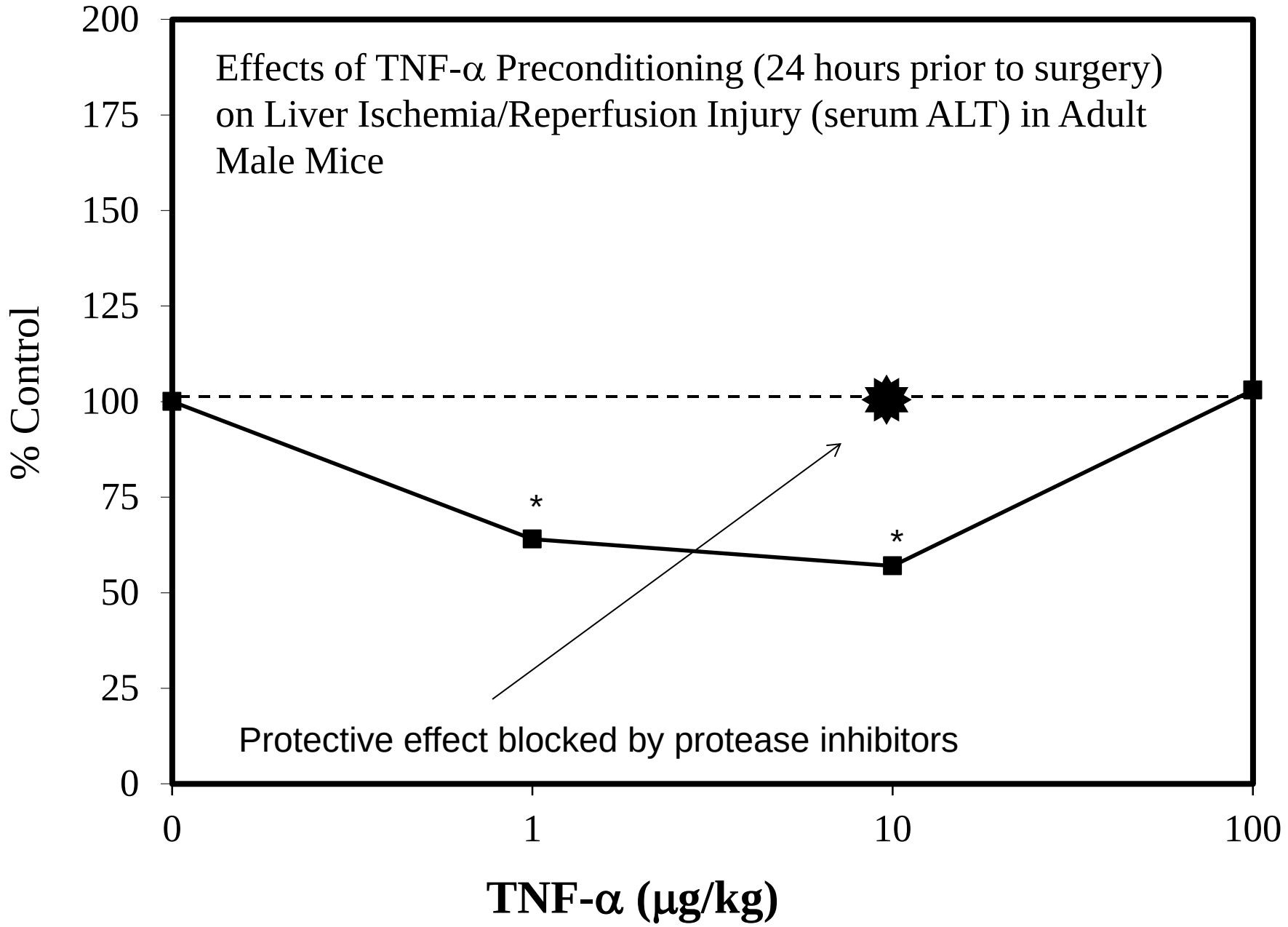

Nitrite Preconditioning In Vitro
Effects of Nitrite Preconditioning (15 minutes prior to ischemia) on Cardiac Damage (myocardial necrosis) in Sprague-Dawley Males *in vitro* Following 30 Minutes of Regional Ischemia and 180 Minutes Reperfusion
% Control
200
175
150
125
100
75
50
25
0
*
*
*
Blocked by NO scavenger; Apoycin, NADPH inhibitor; HMR 1098, a sarcolemma kATP channel blocker; 5HD, mitochondrial kATP channel blocker
0.00
1.00
10.00
30.00
100.00
300.00
Nitrite (µM)

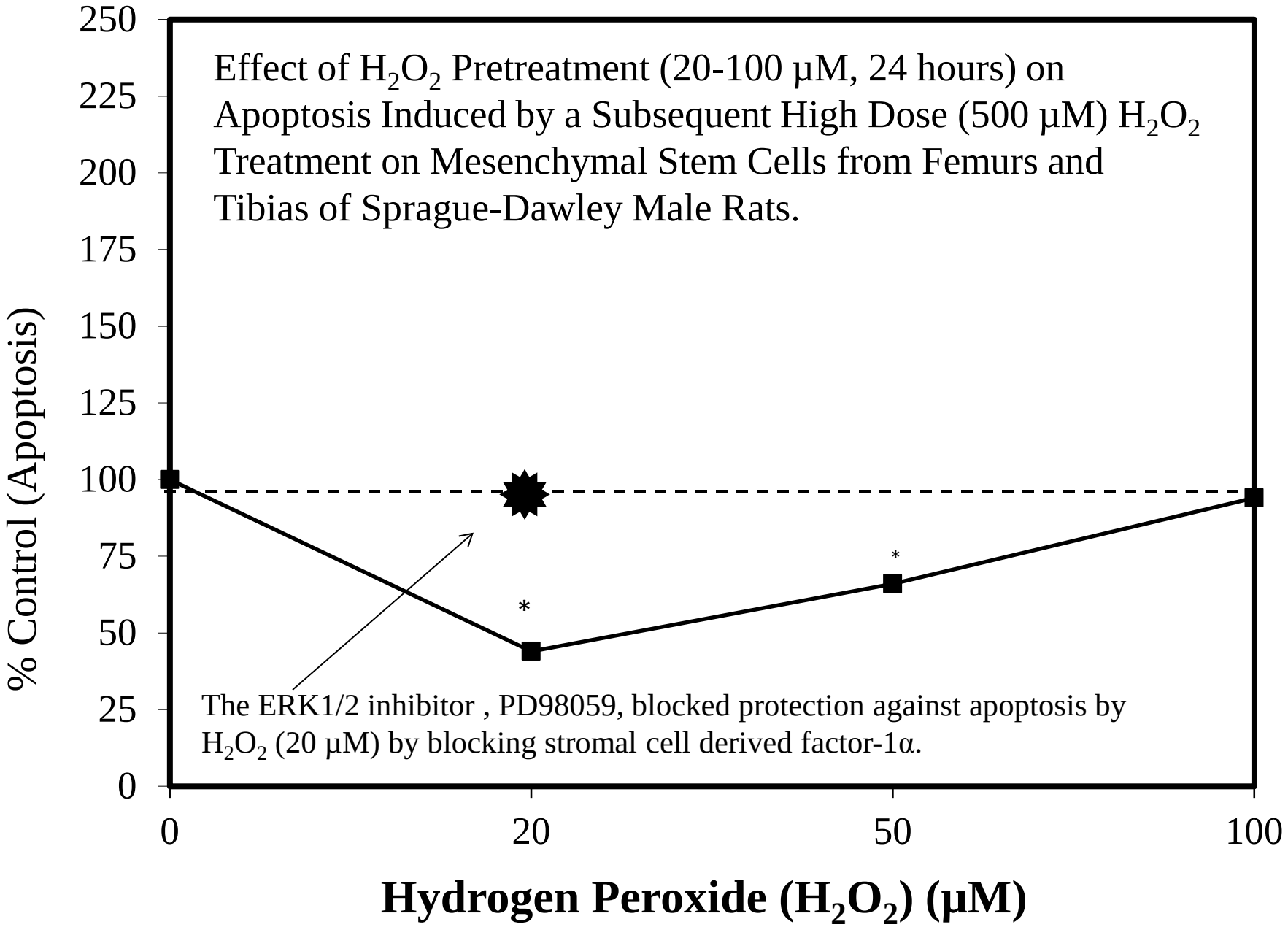

Nitrite Preconditioning In Vivo
Effects of Nitrite Preconditioning (15 minutes prior to ischemia) on Cardiac Damage (myocardial necrosis) in Sprague-Dawley Males *in vivo* Following 30 Minutes of Regional Ischemia and 120 Minutes Reperfusion
% Control
200
175
150
125
100
75
50
25
0
*
*
*
0.00
0.04
0.40
1.00
4.00
7.00
10.00
Nitrite (mg/kg)


Lipopolysaccharide (LPS) Preconditioning Treatment Prevents Stroke Damage in Male C57Bl/6 Mice
% Control
200
175
150
125
100
75
50
25
0
0.00
0.02
0.05
0.10
0.20
0.40
0.80
Damage prevented by TNFα knockout mice; protection prevented by TACE (TNFα converting enzyme) inhibitor
Lipopolysaccharide (LPS) (mg/kg)


Methamphetamine (24 hr) Pretreatment Protects Against 6-OHDA Toxicity in MN9D Cells, a Model of Dopamine Neurons, BcL Response was Blocked by the Akt Inhibitor LY294002
% Control
250
225
200
175
150
125
100
75
50
25
0
0.0
0.1
0.5
1.0
2.0
3.0
Methamphetamine (µM)
Blocked by LY294002, Akt inhibitor
ATP Levels
Cell Viability
Bcl
*
*
*
*


Effects of Preconditioning Schedule (duration/minutes-number of 3 minute cycles-Ischemia) on Renal Damage in Male Wistar Rats Due to Subsequent Prolonged Ischemia (90 min)
Protection blocked by L-NAME, a NOS inhibitor
% Control
200
175
150
125
100
75
50
25
0
0
2
3
4
5
*
*
*
*
Histology
Serum Creatinine
BUN
(Number of 3 Min-Ischemia Cycles)


Effects of TNF-α Preconditioning (24 hours prior to surgery) on Liver Ischemia/Reperfusion Injury (serum ALT) in Adult Male Mice
% Control
200
175
150
125
100
75
50
25
0
*
*
Protective effect blocked by protease inhibitors
0
1
10
100
TNF-α (μg/kg)


Effect of H_2O_2 Pretreatment (20-100 µM, 24 hours) on Apoptosis Induced by a Subsequent High Dose (500 µM) H_2O_2 Treatment on Mesenchymal Stem Cells from Femurs and Tibias of Sprague-Dawley Male Rats.
% Control (Apoptosis)
250
225
200
175
150
125
100
75
50
25
0
0
20
50
100
*
*
The ERK1/2 inhibitor , PD98059, blocked protection against apoptosis by H_2O_2 (20 µM) by blocking stromal cell derived factor-1α.
Hydrogen Peroxide (H_2O_2) (µM)

CONCLUSIONS

- Hormesis is a central biological concept.
- It affects all disciplines utilizing the dose response concept.
- It represents a general adaptive strategy through which biological performance is enhanced and mediated.

CONCLUSIONS

Pre- post-conditioning response = adaptive response = hormetic response

CONCLUSIONS

- The quantitative features of pre- post-conditioning are constrained by the limits of plasticity as described by the hormetic dose response.

CONCLUSIONS

- Preconditioning protective biphasic dose responses can be directly linked to the actions of the conditioning dose based on optimal dosage, temporal relationship, and receptor based and/or cell signaling based mechanisms.

CONCLUSIONS

- Knowledge of the biphasic nature of the preconditioning dose response provides a means to optimize therapeutic applications.

- Hormesis provides both the theoretical basis and the molecular foundations to create biological shields to protect against chemical, radiological, and microbial threats.