COEURative

Coeurative's Goal is to Create Curative Strategies for Cardiovascular Diseases Associated with Cellular Hypoxia

Focus on New Treatments for Refractory Angina Pectoris

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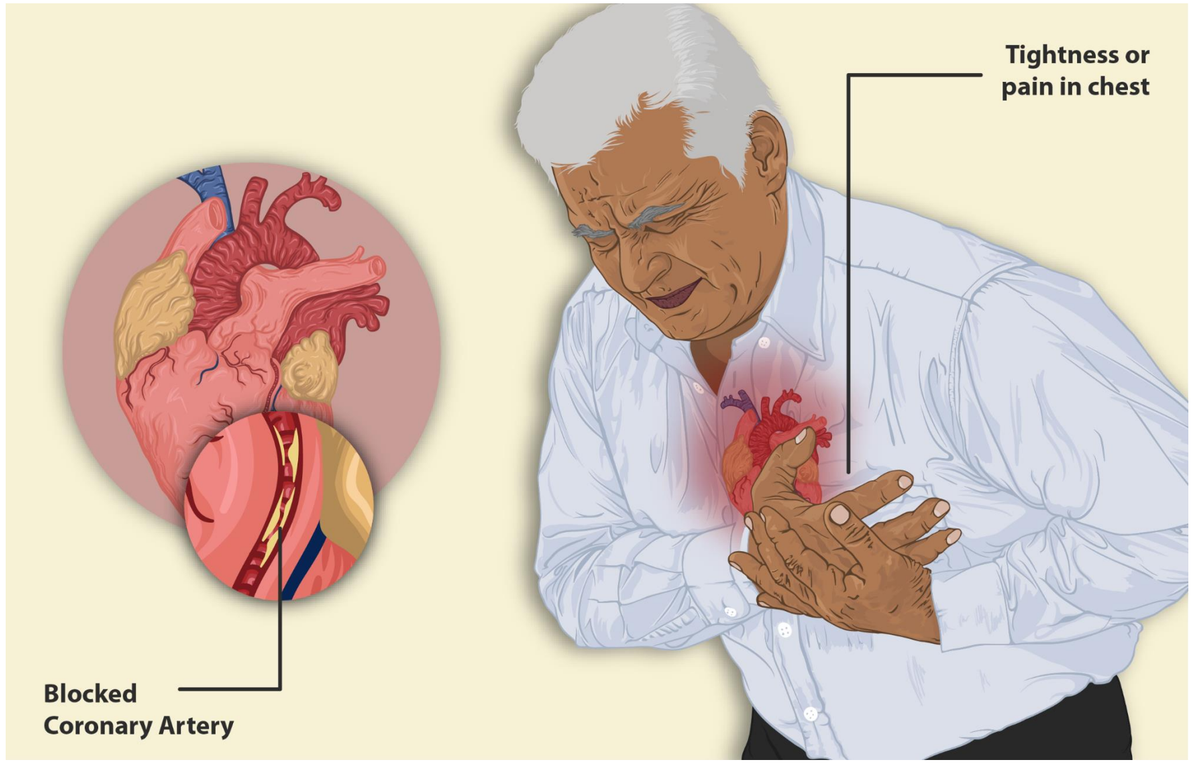
Hypoxia & Inflammation are Key Factors in the Development of Coronary Heart Disease and Angina Pectoris that are treated with Nitric Oxide

- Hypoxia is a clinically significant lack of oxygen
- Cardiac hypoxia leads to **angina pectoris** and **CHD**
- Angina pectoris is a symptom complex often related to narrowing of the coronary arteries and a reduction in blood flow to the heart that can lead to:
  - Chest pain
  - Shortness of breath
  - Dizziness
  - Nausea
- Hypoxia leads to increased expression of inflammatory cyclooxygenase-2
- Hypoxia and inflammation in heart diseases with different etiologies may be reversed by the same molecule: Nitric Oxide (NO) found in NTG
  - Oral nitroglycerine (NTG) opens coronary arteries by releasing NO



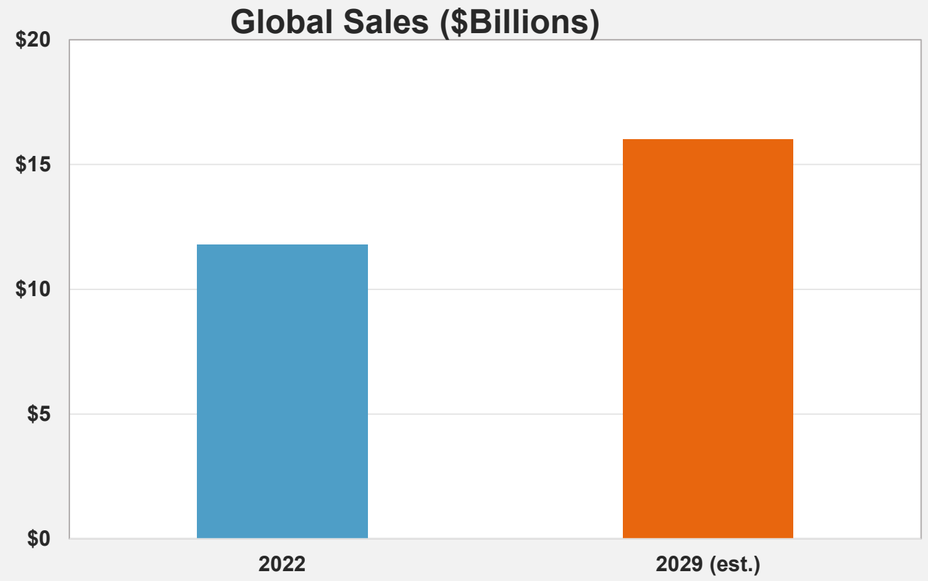
CR-0305, A New Treatment for Angina Pectoris Represents a Significant Market Opportunity

A Large Market Opportunity

10 million Angina patients in US

21% of Angina patients have a monthly attack

Annual mortality 3% to 17%



Source: Blumenthal et al., JAMA 2021 and MMR Angina Pectoris Market Report

Current Drug Treatment is Inadequate

Nitrates	**Tachyphylaxis/Tolerance** (limiting duration of action)
Calcium Channel Blockers	**Common side effects** include edema and constipation
Beta Blockers	**Significant side effects** in patients with COPD or diabetes
Anti-platelets	**Bleeding**
Ranolazine	**Mechanism of action unknown** and **QT prolongation**

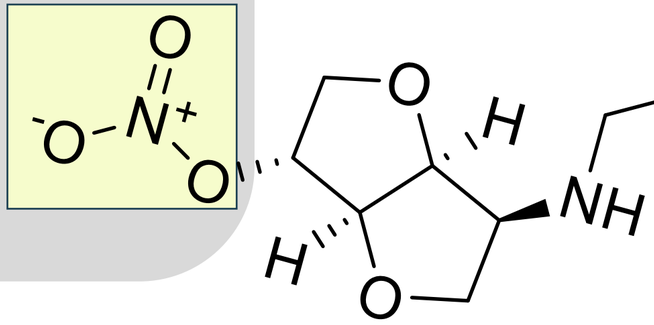
CR-0305 is Designed to Deliver a ONE-TWO Punch in the Treatment of Angina and is MORE than an NO donor

ONE

Nitrate donates nitric oxide to quickly dilate arteries and provide immediate relief by reversing hypoxia

TWO

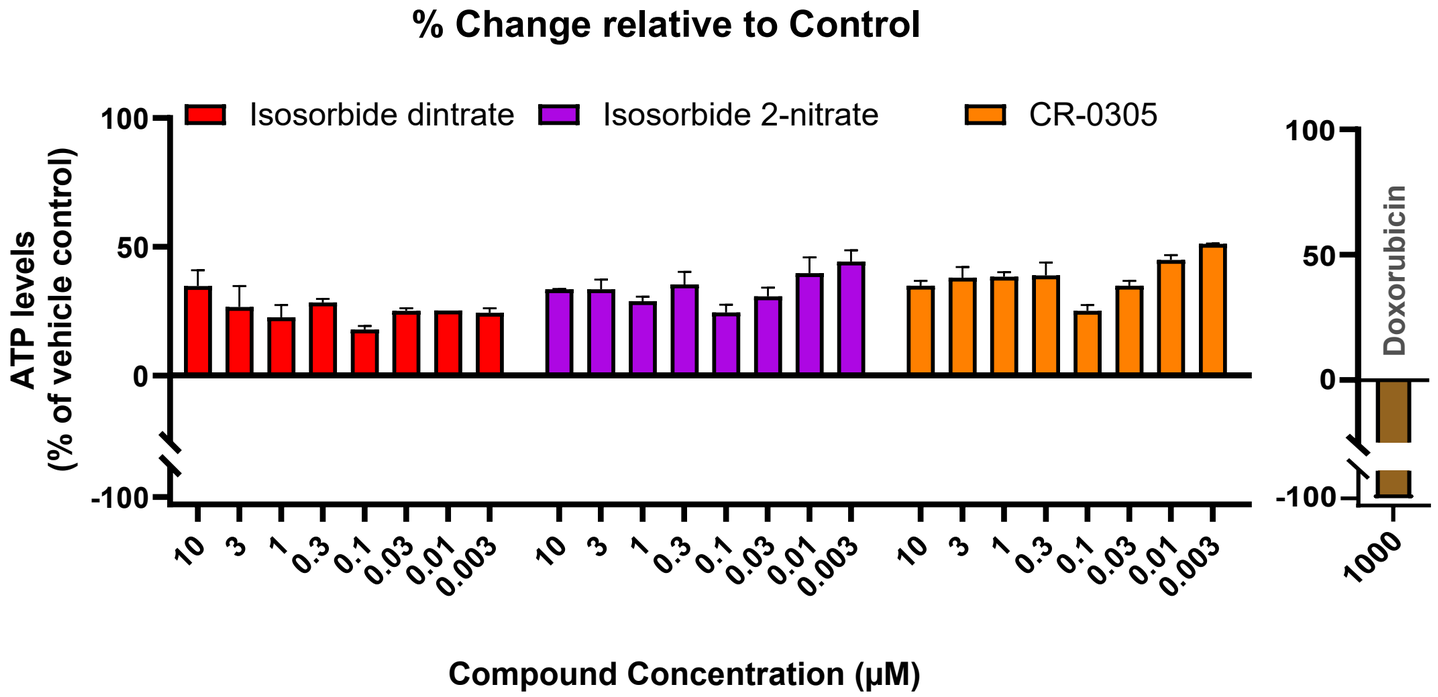
Glycolamide (urea analog) **facilitates NO formation by the cell itself**



CR-0305

Source: US Patents #10,501,471, #10,913,748 and #11,779,560

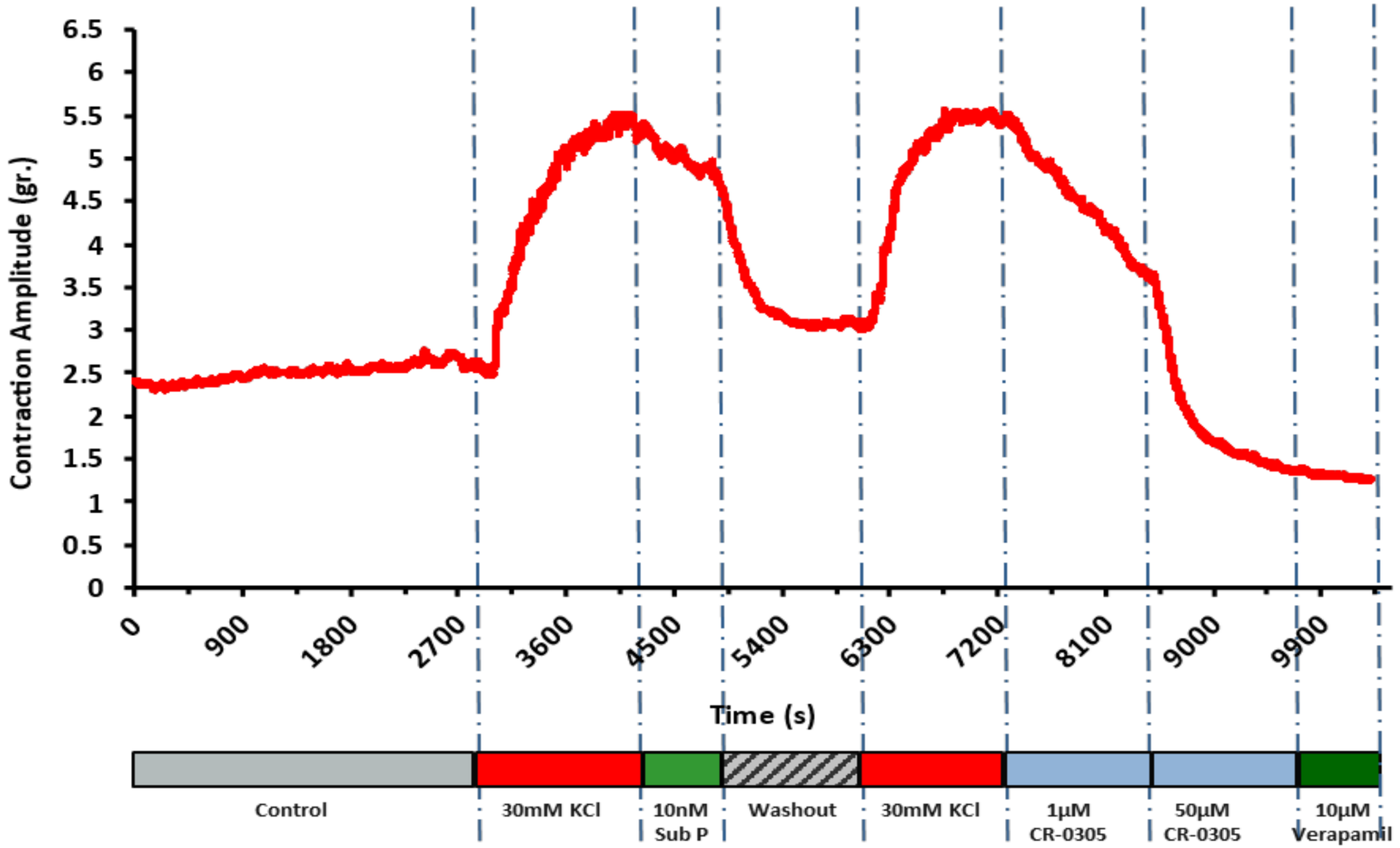
Coeurative Compounds Demonstrate Low Toxicity



Source: Coeurative Laboratory and Cayman Chemical Co.

HMEC-1 cells were treated with Coeurative compounds, vehicle control (0.1% DMSO), or positive control (doxorubicin) at conditions indicated and cultured for 18 hours. There was no decrease in cellular ATP levels (a measure of cell health) in the organic nitrates, including CR-0305, compared with vehicle control.

CR-0305 Relaxes the Human Coronary Artery *ex vivo*



Coronary artery relaxation was observed when CR-0305 was applied to a human coronary artery in a bath.

CR-0305 was strong enough to reverse the KCl control vasoconstriction

Source: Coeurative Laboratory and AnaBios

Coeurative is Developing Patent-Protected Molecules That Are Expected to be Potent and Selective in Coronary Disease

Current Status

- CR-0305 is currently undergoing development using nondilutive funding from the NIH SBIR program and the Virginia Commonwealth Commercialization Fund
- Medicinal chemistry under development in concert with Cayman Chemical Company

IP Protection

- Protected under US Patents 10,501,471 (filed June 2019), 10,913,748 (October 2019), and 11,779,560 (March 2021)
- Protected by international patent applications through PCT/US2019/058241 (October 2019) and PCT/US2021/024540 (March 2021)

Next Steps

- Evaluate CR-0305 in human coronary arteries *ex vivo* and human cell culture *in vitro* to evaluate mechanism of action
- Extend initial studies indicating lack of toxicity to more detailed studies of absorption, distribution, metabolism, and excretion in animal models

Significant Progress as of 2025 – Future Development Plan

2025

- Dedicated lab facilities established
- Patents Issued
- *In vitro* Toxicity testing passed
- *Ex vivo* experiment confirms vasodilatory properties
- Over $1.6 M raised to date including private investments, SBIR and Virginia CCF funding

2027

- File IND application for CR-0305
- Phase 1 clinical trials
- Preclinical testing for other cardiovascular indications
- Establish management team

2030

- File NDA for CR-0305 using 505(b)(1) pathway
- Launch CR-0305 for the treatment of Angina (with a partner)
- IPO less likely in current environment
- Licensing or acquisition more likely

Executive Summary

- Coeurative is led by its founder, John Schmedtje, with over 35 years of experience as a teacher and physician scientist focused on the study of cardiovascular disease
- Angina pectoris is an important clinical syndrome that affects 10 million patients in the US alone
- Current treatments are inadequate due to limited potency, significant side effects, and tachyphylaxis (tolerance)
- Novel pharmaceuticals to address refractory angina pectoris are needed
- CR-0305 has demonstrated significant vasodilatory properties in *ex vivo* studies of human coronary arteries and appears to enable human coronary artery cells to facilitate the formation of vasodilatory nitric oxide (NO)
- CR-0305 has patent protection through 2039 before extension

Coeurative is raising funding to complete preclinical work and push past the FDA IND (Investigational New Drug) application into Phase 1 of clinical investigation

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