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Creating Curative Strategies for Diseases Associated with Cellular Hypoxia

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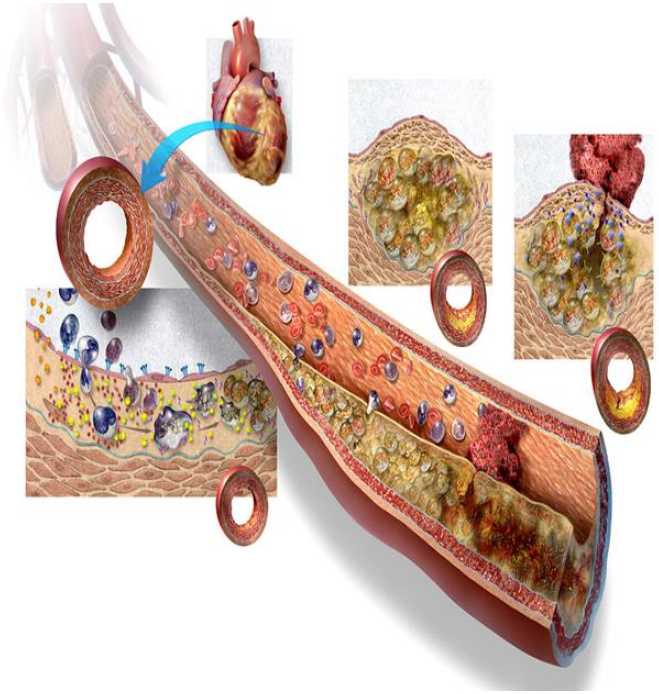
8 April 2023

Problem: Atherosclerotic Cardiovascular Disease

- ASCVD (atherosclerotic cardiovascular disease) will not disappear in our lifetimes.
- According to the American Heart Association Heart Disease and Stroke statistics, cardiovascular disease in general, including coronary heart disease (CHD) along with heart failure, arterial disease, stroke, and hypertension
  - is mostly secondary to ASCVD.
  - between 2015 and 2018, 127 million or 49.2% of US adults had some form of CVD, not counting peripheral vascular disease.
  - will lead to total annual US costs of $1.1 Trillion in 2035.
  - causes 18 million deaths/year worldwide and will cause 22 million in 2030.
- There is no vaccine for ASCVD.
- We must improve upon the pharmaceutical options for treatment presently available.



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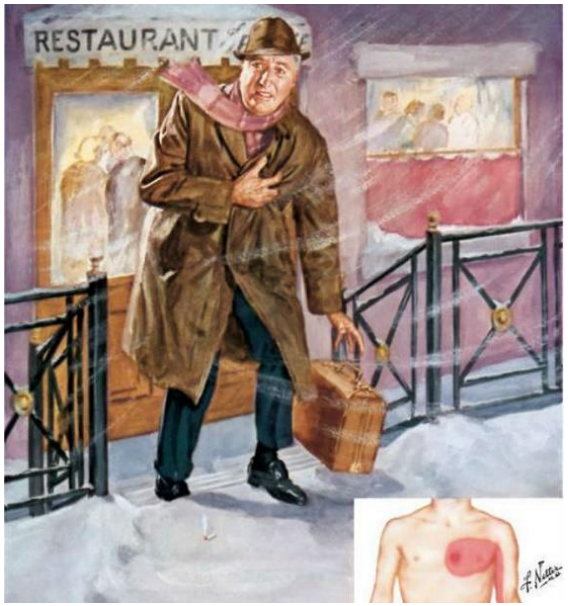
The Disease: Hypoxia and Inflammation are key factors in development of Coronary Heart Disease

- Cardiac hypoxia leads to angina pectoris.
  - Nitric Oxide (NO) from oral nitroglycerine (NTG) opens coronary arteries.
- 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, NO.



- Nitric Oxide (NO) is donated (chemically released) by NTG to relax blood vessels quickly and briefly.
- Longer acting NO donors like isosorbide mononitrate are relatively weak.
- Novel NO donors that target hypoxia should have more therapeutic value in CHD.

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CR-0202 and CR-0305: Custom-Designed NO donors for CHD

- Nitrate is an NO donor that dilates arteries and may protect against ischemia.
- Glycolamide is a urea analogue that can also facilitate NO formation.
- Targeted delivery of an oral agent that donates NO is desired for both ischemic preconditioning and to restore oxygenation.

CR-0202 and CR-0305 can deliver a "One-Two" punch:

-Nitrate group dilates vessels and reverses hypoxia

-Glycolamide optimizes NO production

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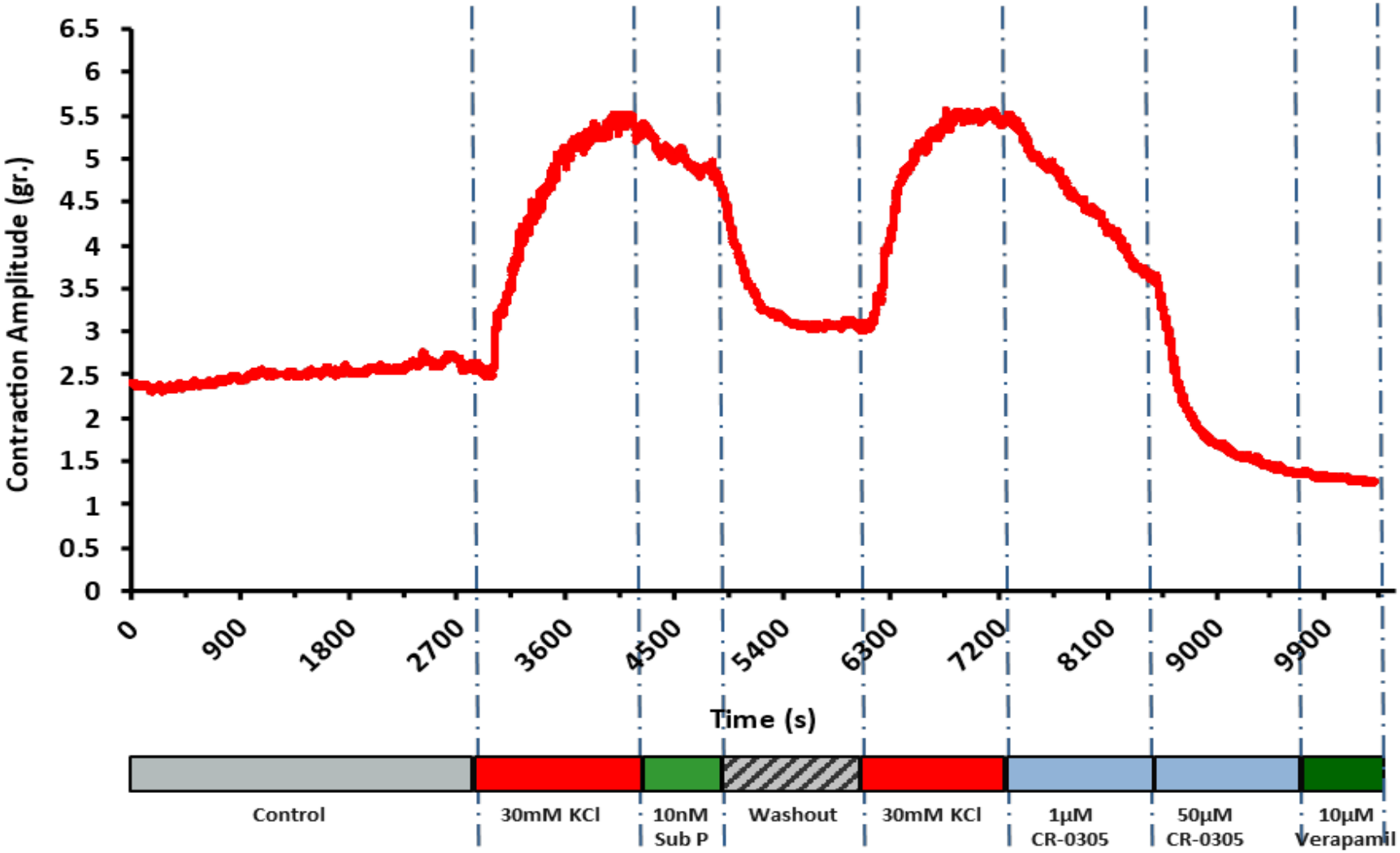
CR-0305 Relaxes the Human Coronary Artery *ex vivo*



Representative Time Course Graph of Contraction Amplitude

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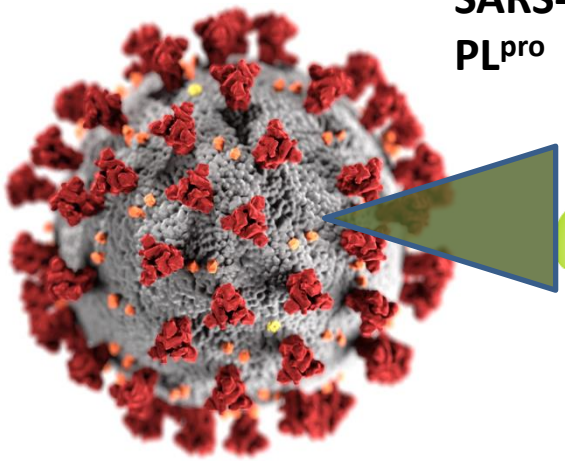
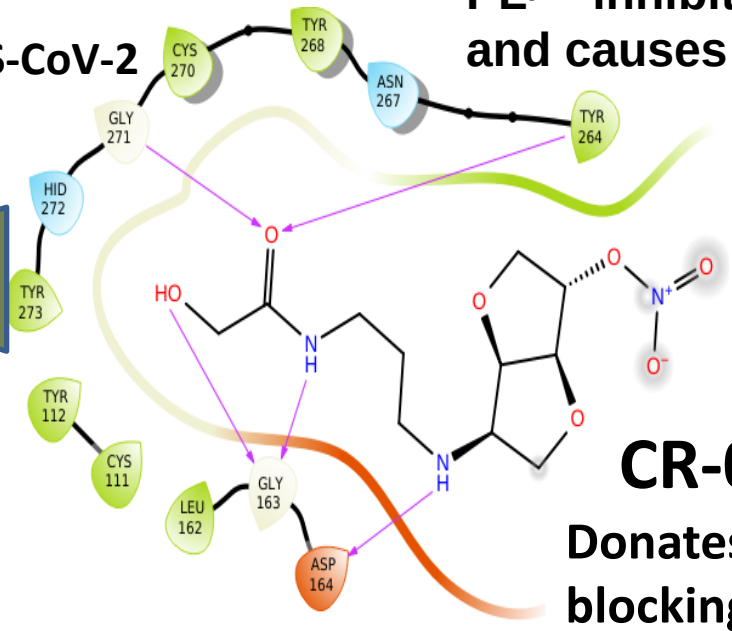
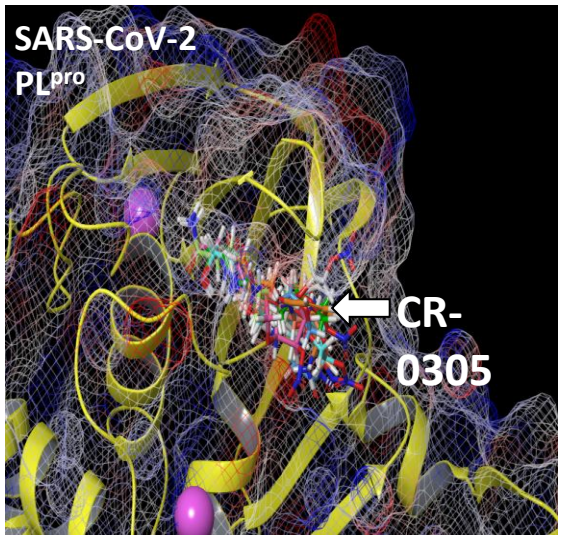
Antiviral Indication: CR-0202 and CR-0305 Act As NO Donors and PL^{pro} Inhibitors on SARS-CoV-2



SARS-CoV-2 PL^{pro}

PL^{pro} inhibits cell defenses and causes viral replication





CR-0305

Donates NO while blocking PL^{pro} catalytic site

Nitrate

Isosorbide

Glycolamide

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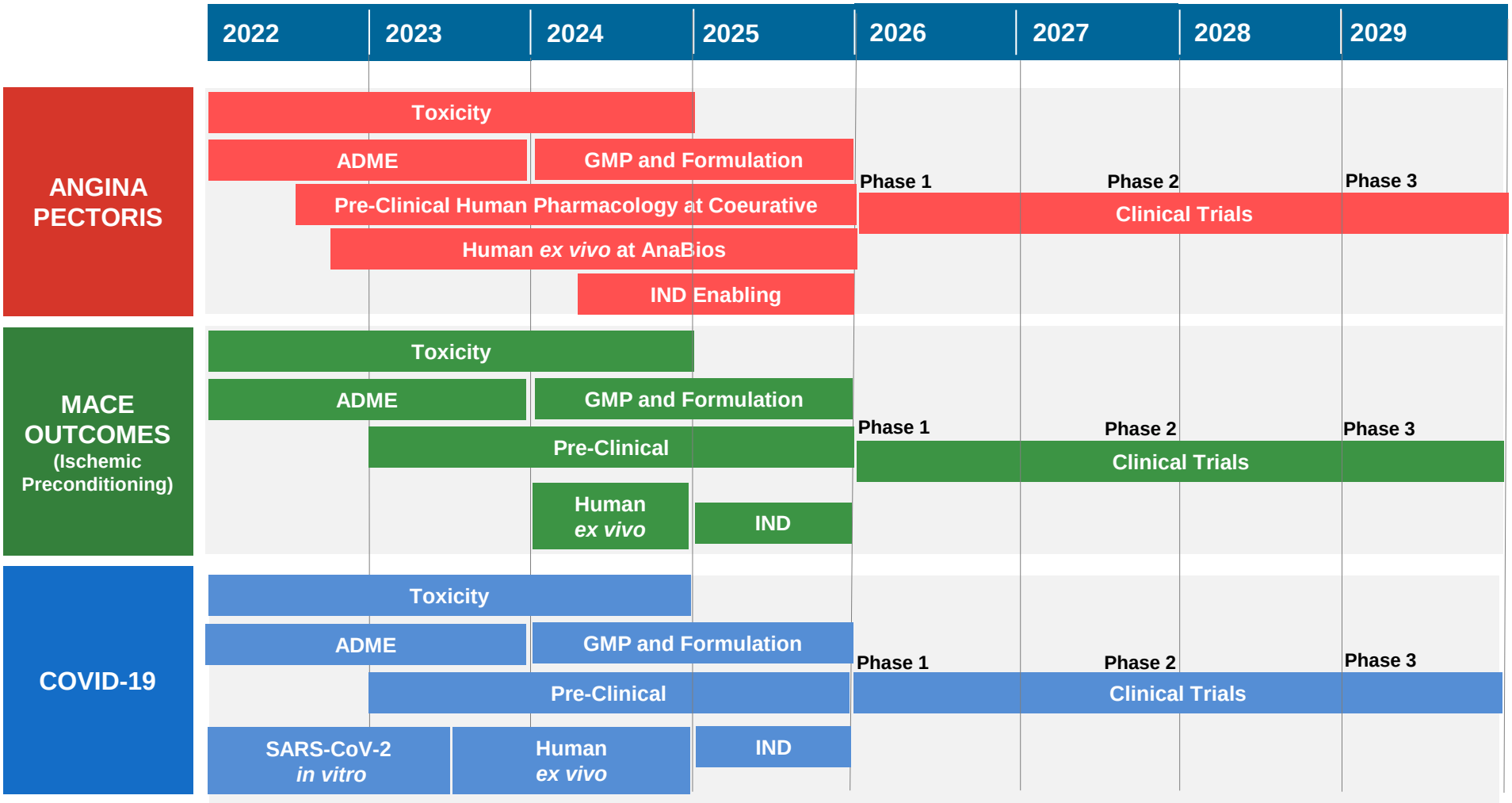
Milestones Achieved

- Company structure and dedicated lab facilities established.
- CR-0202 and CR-0305 synthesized for *in vitro* and *ex vivo* study.
- US Patents No. 10,501,471 and 10,913,748 issued.
  - Nonprovisional US Patent Application 17,211,778 filed.
  - International Patent Applications PCT/US19/58241 and PCT/US21/24540 filed with national phases underway.
- "A Nitric Oxide Donor Binds to SARS-CoV-2 Papain-Like Protease with Therapeutic Implications" presented to American Heart Association.
  - Circulation, 2021; 144:A10067. https://doi.org/10.1161/circ.144.suppl_1.10067
- Toxicity tests passed *in vitro.* ADME experiments justify oral administration.
  - Human cell culture studies of mitochondrial function and ATP formation reveal little to no toxicity of CR-0202 and CR-0305 at five times expected peak human plasma concentration.
- Human coronary artery rings studied *ex vivo* with CR-0305 confirm that it is a potent coronary vasodilator at physiologically relevant concentrations.
- Private investment to date: $920,000.

Development Plan

Three indications for CR-0202 and CR-0305 are in pipeline. Angina Pectoris is prioritized.



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The Founder

- MD, 1981: Graduate of Honors Program in Medical Education at Northwestern University
- MPH, 1983: Harvard School of Public Health
- Internal Medicine Residency, 1986: Baylor College of Medicine
- Cardiology Fellow, 1991: Medical College of Virginia
- Faculty appointments at Baylor, University of Texas Medical Branch, Wake Forest University School of Medicine
- Published on hypoxia in medical science journals with high impact factors such as Circulation Research and Journal of Biological Chemistry
- Winner of the 1996 Cournand & Comroe Young Investigator Prize from the American Heart Association for cardiopulmonary research.
- Team player with a thirty-year track record of collaboration with the pharmaceutical industry on clinical trials and drug development.

COEURATIVE, Inc. is creating curative strategies for diseases associated with cellular hypoxia.

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