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Creating Curative Strategies for Diseases Associated with Cellular Hypoxia

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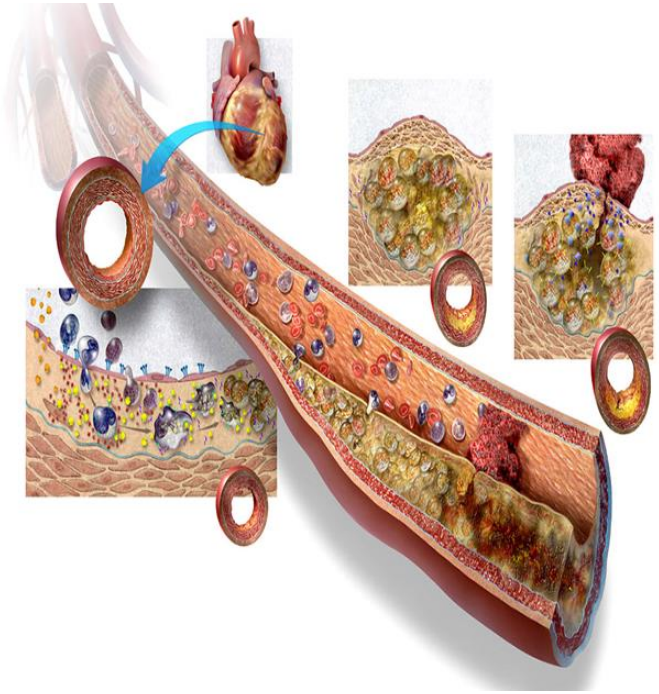
Problem: Atherosclerotic Cardiovascular Disease

- ASCVD (atherosclerotic cardiovascular disease) will not disappear in our lifetimes.
- According to the American Heart Association Heart Disease and Stroke statistics, cardiovascular diseases in general (including coronary heart disease, heart failure, arterial disease, stroke, and hypertension)
  - are mostly secondary to ASCVD.
  - are found in 92 million Americans over the age of 20, or 36% of the adult population.
  - will lead to total annual US costs of $1.1 Trillion in 2035.
  - cause 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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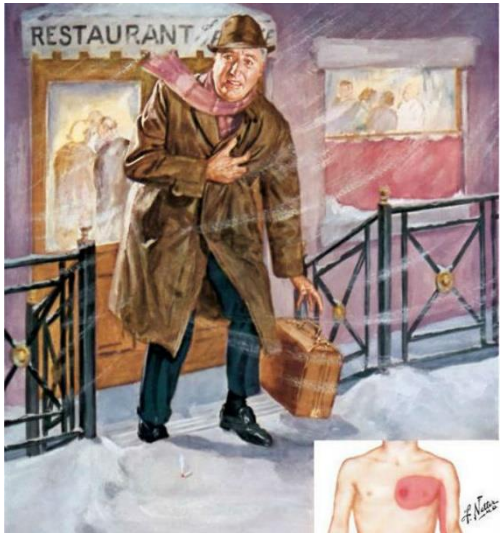
The Disease: Hypoxia and inflammation are key factors in development of ASCVD

- Cardiac hypoxia leads to angina pectoris.
  - Nitric Oxide (NO) from oral NTG opens coronary arteries.
- Inflammation in the vascular endothelium is the first sign of ASCVD.
- Hypoxia and inflammation in heart diseases with very different etiologies may be reversed by the same molecule, NO.



- Nitric Oxide (NO) is donated by NTG (Nitroglycerin) to relax blood vessels quickly and briefly.
- Longer acting NO donors like isosorbide mononitrate are relatively weak.
- Targeted NO donors that reduce inflammation should provide a more long-lasting effect on ASCVD.

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

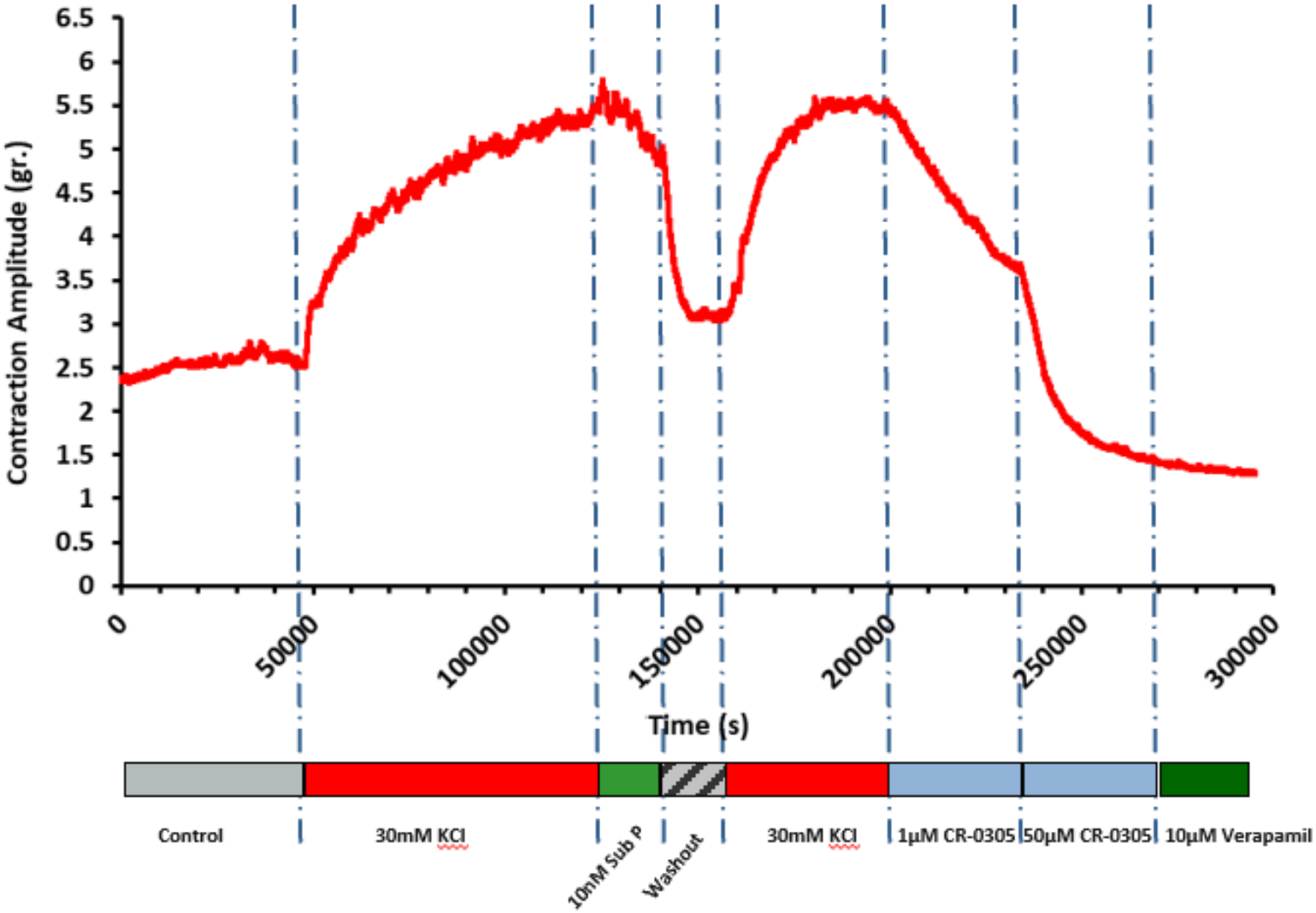
- Nitrate is an NO donor that dilates arteries and may protect against ischemia.
- Glycolamide is a urea analogue that can also facilitate NO formation.
- Targeted delivery of an oral agent that donates NO is desired for both ischemic preconditioning and to restore oxygenation.

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

-Nitrate group dilates vessels and reverses hypoxia

-Glycolamide optimizes NO production

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



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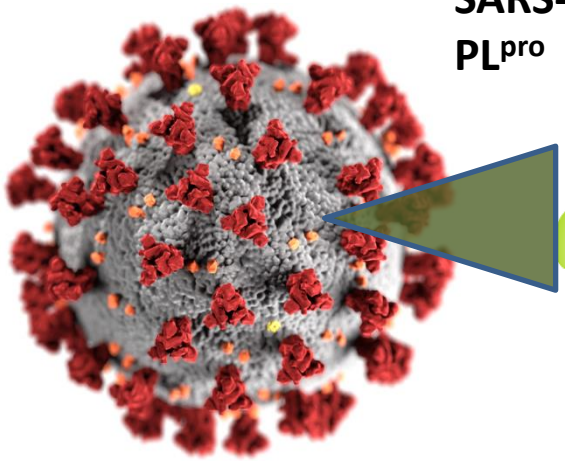
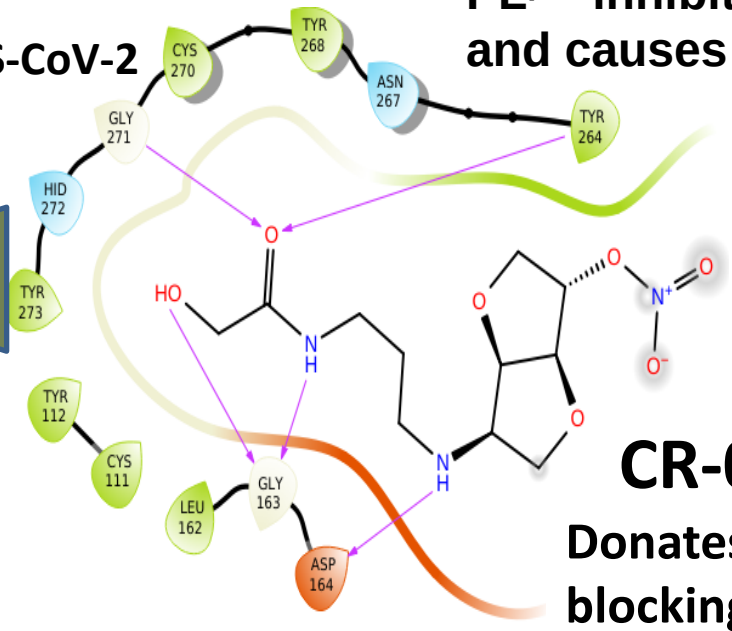
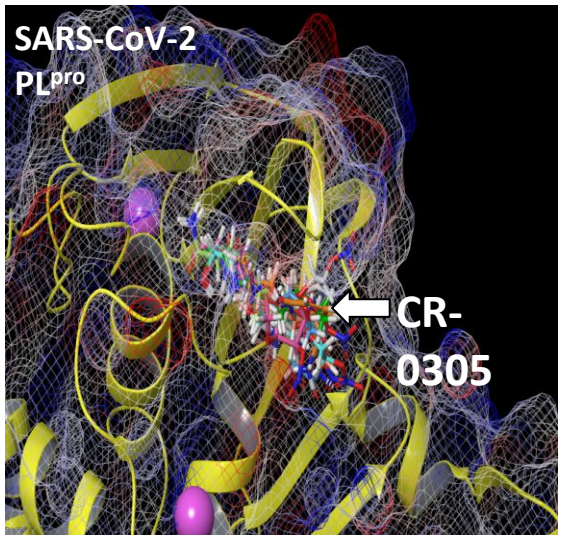
CR-0202 and CR-0305 Are Also NO Donors and PL^{pro} Inhibitors for SARS-CoV-2 (virus of COVID-19)



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* study.
- Patent 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.
- "A Nitric Oxide Donor Binds to SARS-CoV-2 Papain-Like Protease with Therapeutic Implications" presented to American Heart Association.
  - Circulation, 2021; 144:A10067 OR https://doi.org/10.1161/circ.144.suppl_1.10067
- Toxicity tests passed *in vitro.* ADME experiments promising for oral use.
  - 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.
- Drug screening in mammalian cells infected by SARS-CoV-2 reveals that CR-0305 and CR-0202 reduced viral infection at a concentration near to that of known PL^{pro} inhibitor GRL-0617.
- Private investment to date: $845,000.

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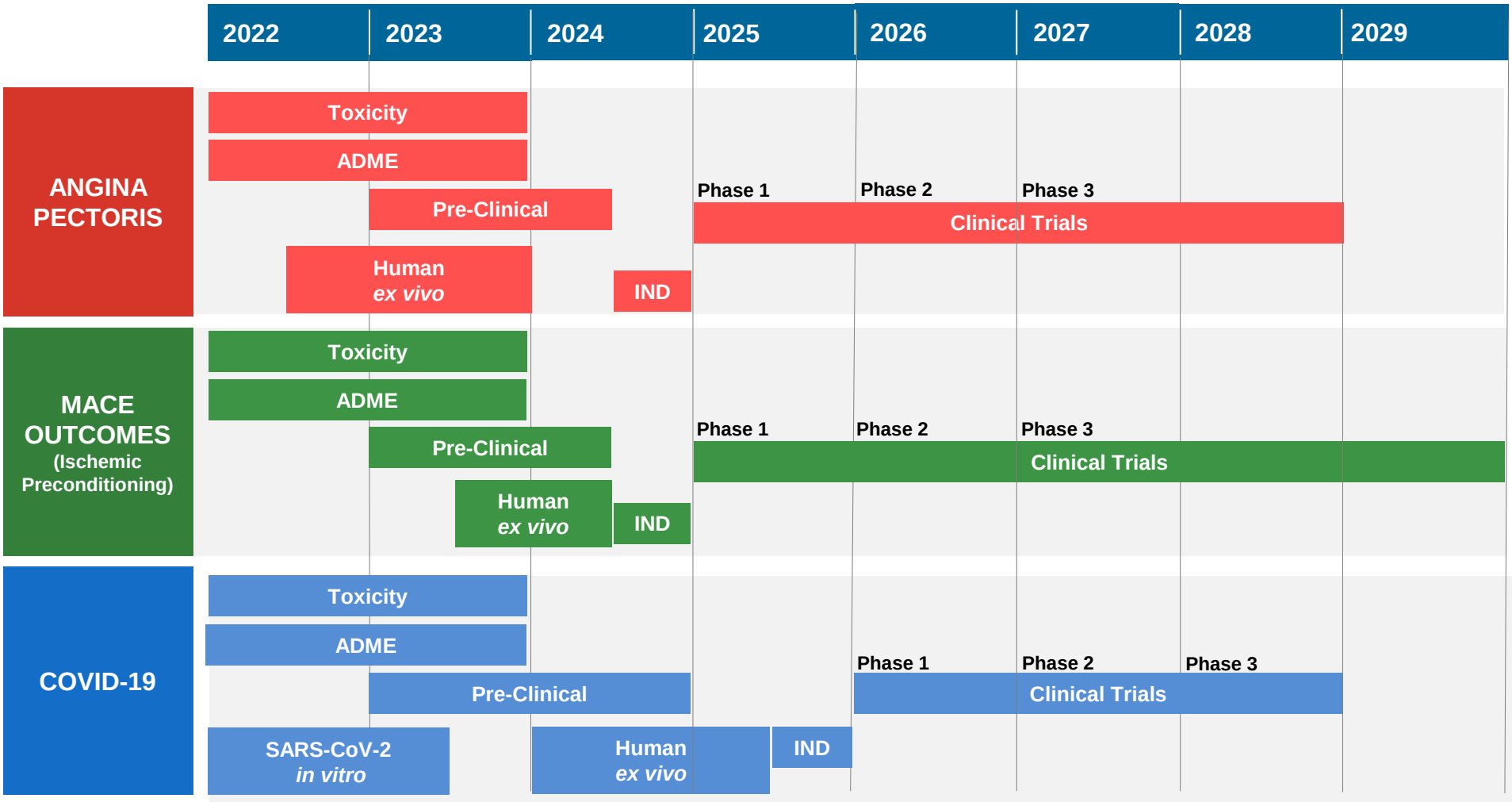
Accelerated Development Plan

Contingent on Funding for Development of the Indications for CR-0202 and CR-0305



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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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