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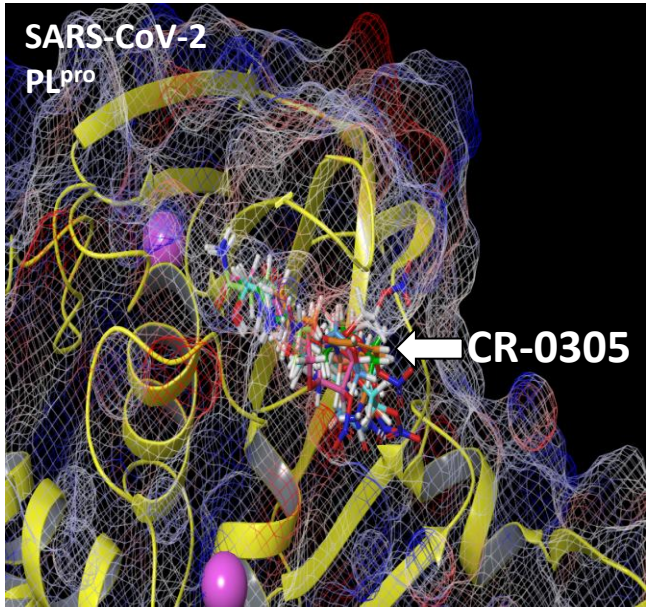
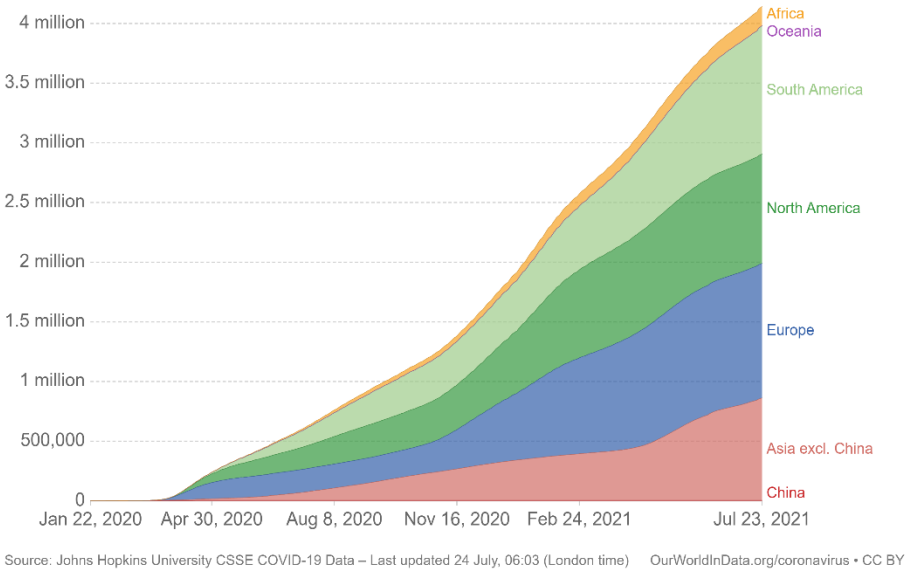
Creating Curative Strategies for Diseases Associated with Cellular Hypoxia



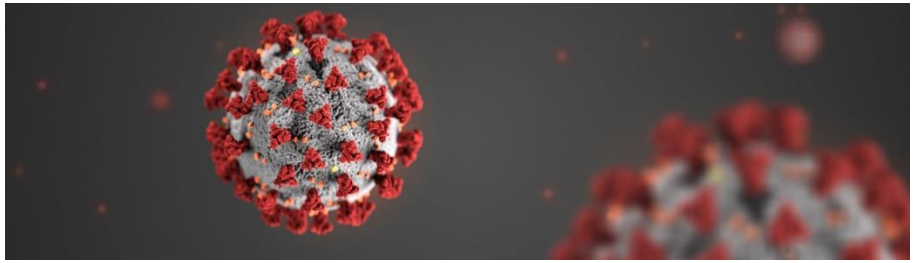
John F. Schmedtje Jr., MD
Founder, President and CEO

Problem: COVID-19, caused by SARS-CoV-2

- SARS-CoV-2 will not disappear in our lifetime, and will evolve
- Now 193 million cases, over 4 million deaths (Johns Hopkins, July 24, 2021)
- Vaccines diminish morbidity and mortality, but:
  - data on long term outcomes not available yet
  - limited community acceptance
- Pharmaceutical treatments suboptimal:
  - Remdesivir has a small effect on outcomes.
  - Simply administered oral antivirals needed.



Cumulative Cases



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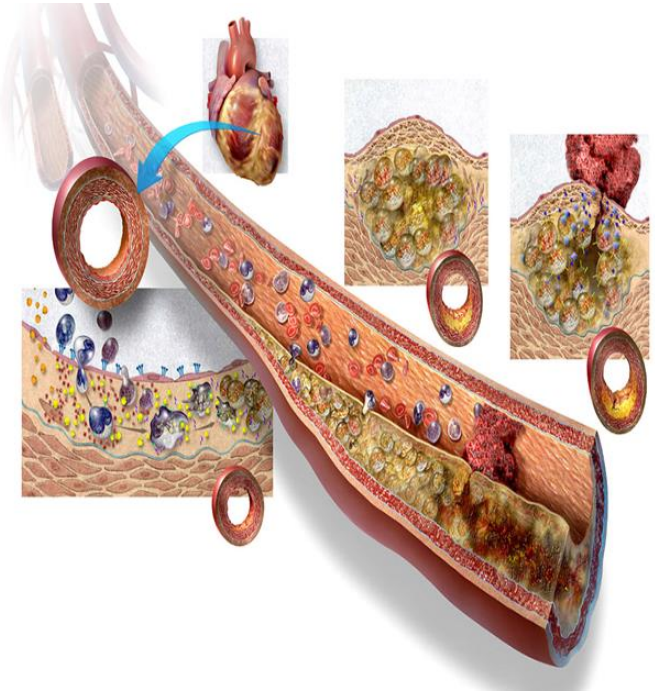
Problem: Atherosclerotic Cardiovascular Disease

- ASCVD will not disappear in our lifetime.
- 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 and no cure for ASCVD.
- Pharmaceutical and surgical treatments available are extensive, but limited.



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The Diseases: Hypoxia and inflammation are key factors in both COVID-19 and ASCVD

- Cardiac hypoxia leads to angina pectoris.
  - Nitric Oxide (NO) from oral NTG opens coronary arteries.
- Inflammation in COVID-19 leads to heart failure.
  - Dissolved NO gas appears antiviral for SARS viruses.
- 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.

Targeted NO donors should mitigate the impact of infection and hypoxia in COVID-19 while ameliorating ASCVD.

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Solution: CR-0305 is a Nitric Oxide Donor

- 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-0305 delivers a "One-Two" punch:

-Nitrate group dilates vessels and reverses hypoxia

-Glycolamide optimizes NO production, targets SARS-CoV-2 and blocks PL^{pro}

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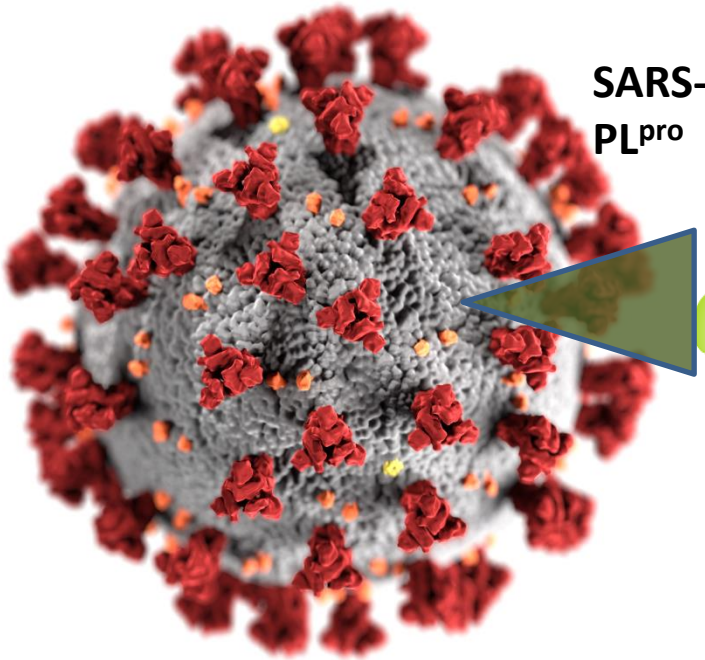
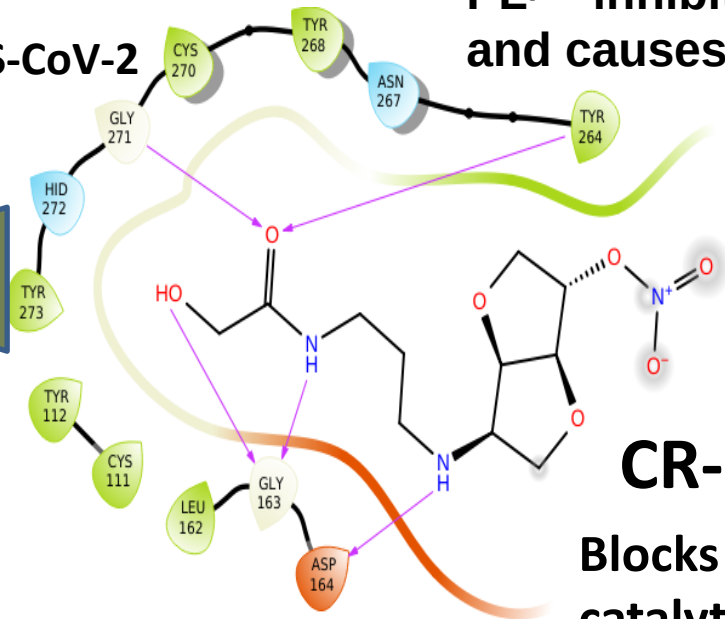
Solution: CR-0305 delivers a Nitric Oxide Donor and a PL^{pro} Inhibitor to SARS-CoV-2



SARS-CoV-2 PL^{pro}

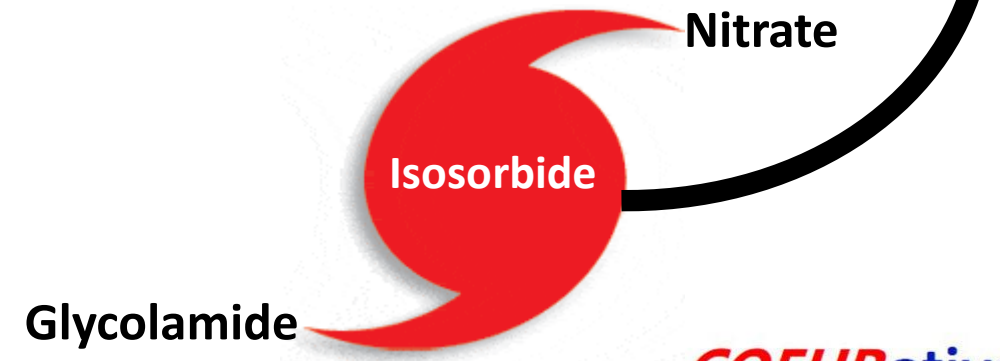


PL^{pro} inhibits cell defenses and causes viral replication

CR-0305

Blocks PL^{pro} catalytic site

- CR-0305 is comparable to the known SARS-CoV-2 PL^{pro} inhibitor GRL-0617 in binding PL^{pro} *in silico*



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Milestones Achieved

- Company structure and dedicated lab facilities established.
- 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.
- "Novel Experimental Therapeutics For COVID-19 Derived From A Nitric Oxide Donor" presented at American Heart Association Nov. 13, 2020.
  - https://doi.org/10.1161/circ.142.suppl_3.13295
- CR-0202 and CR-0305 synthesized for *in vitro* study.
- Toxicity tests passed *in vitro.* ADME experiments underway.
  - 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 at Boston University reveals 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: $448,000.
  - New Series Seed raise underway: $400,000 sought.

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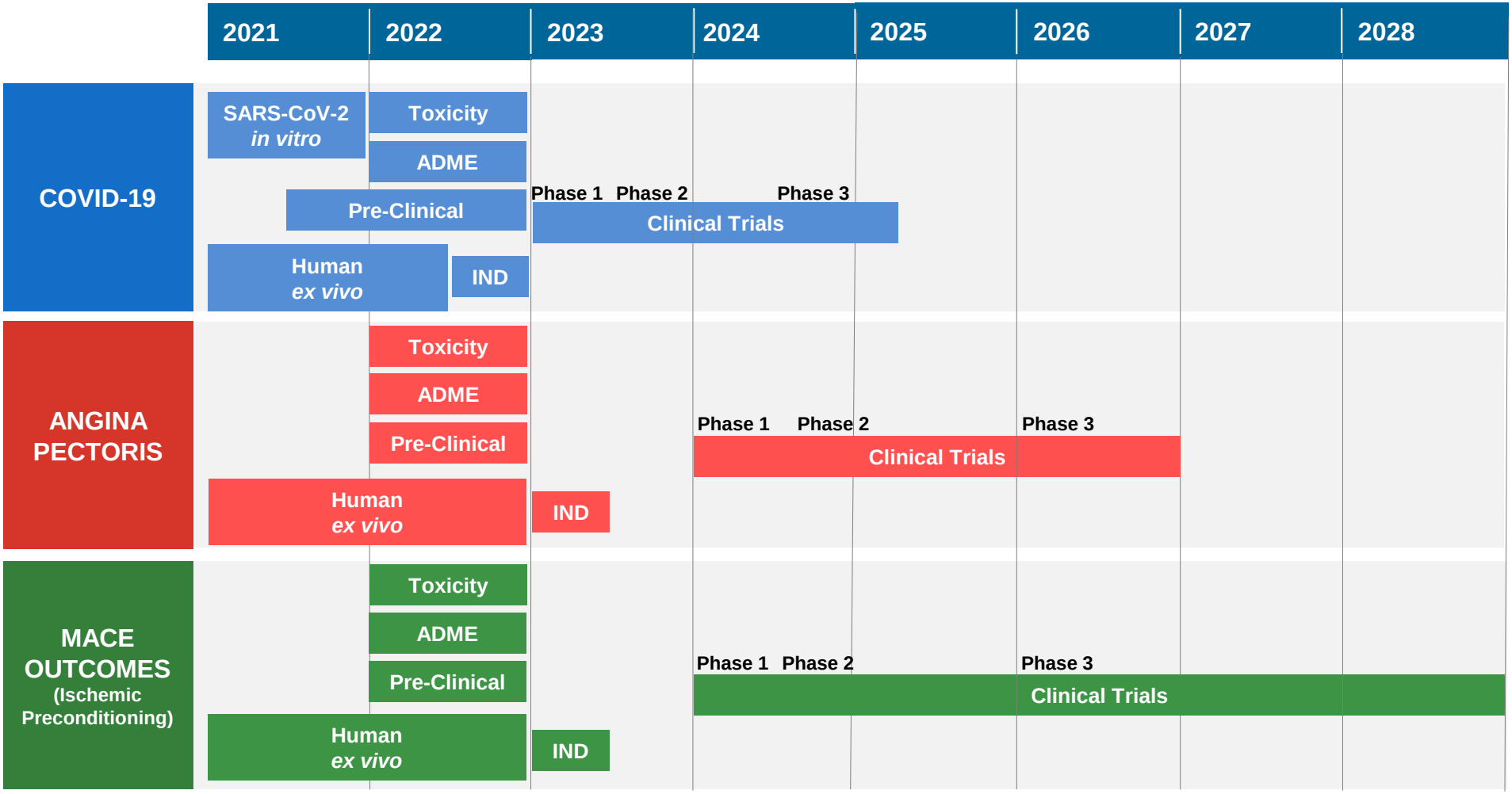
Accelerated Development Plan

Contingent on Funding for the Three Proposed Indications for 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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