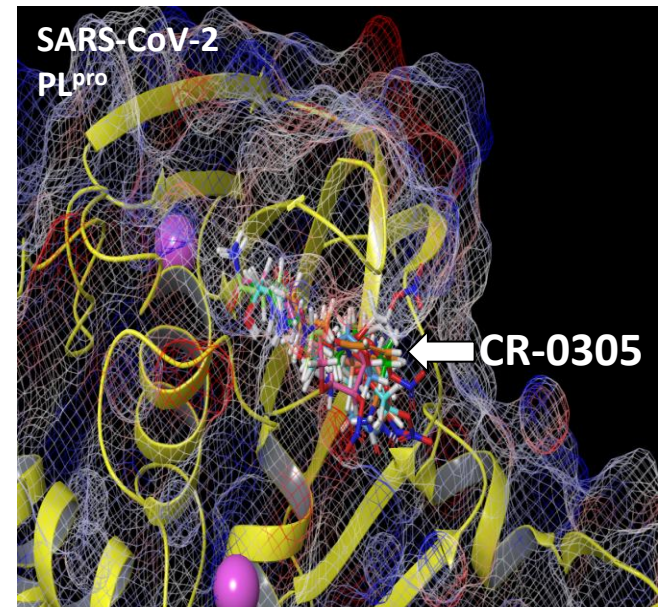


COEURative

Creating Curative Strategies for Diseases
Associated with Cellular Hypoxia

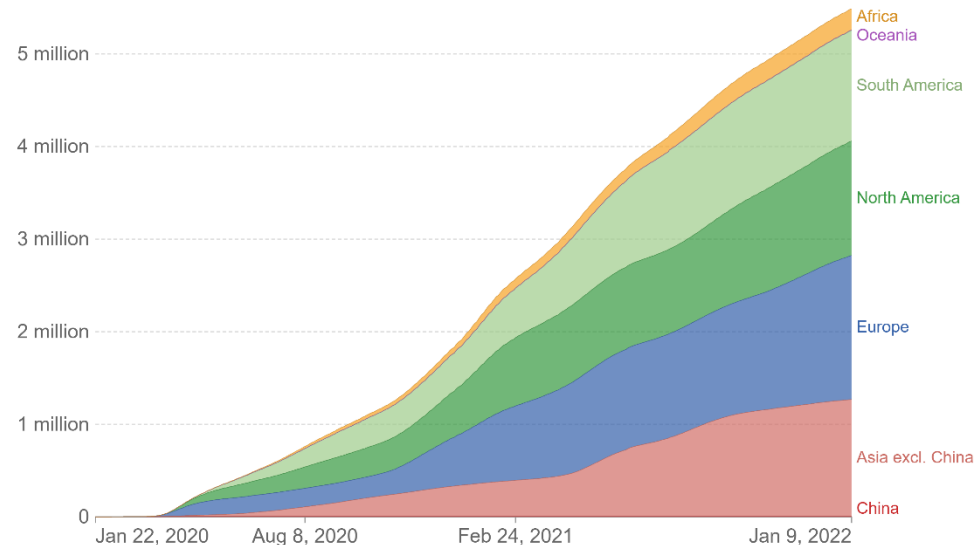


John F. Schmedtje Jr., MD
Founder, President and CEO

The proprietary compounds described in this presentation are protected under US Patents 10,501,471 and 10,913,748, Nonprovisional US Patent Application 17,211,778, and International Patent Applications PCT/US19/58241 and PCT/US21/24540
January 10, 2022

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

- SARS-CoV-2 will not disappear in our lifetime, and will evolve
- 307 million cases, 5.49 million deaths and counting (Johns Hopkins, January 10, 2021)
- Vaccines diminish morbidity and mortality, but:
 - Data on long term outcomes not available yet
 - Finite community acceptance
- Antivirals increasingly important:
 - IV Remdesivir (Veklury)
 - IV Monoclonal antibody “cocktails”
 - Oral Molnupiravir (Lagevrio)
 - Oral PF-07321332/Ritonavir (Paxlovid)
 - Oral Brequinar



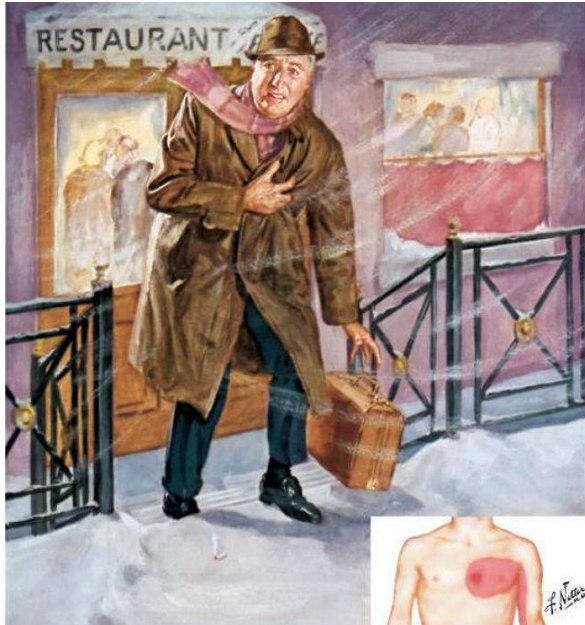
Source: Johns Hopkins University CSSE COVID-19 Data – Last updated 10 January, 16:05 (London time)
OurWorldInData.org/coronavirus • CC BY

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.



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.

Solution: CR-0305 is a Nitric Oxide Donor

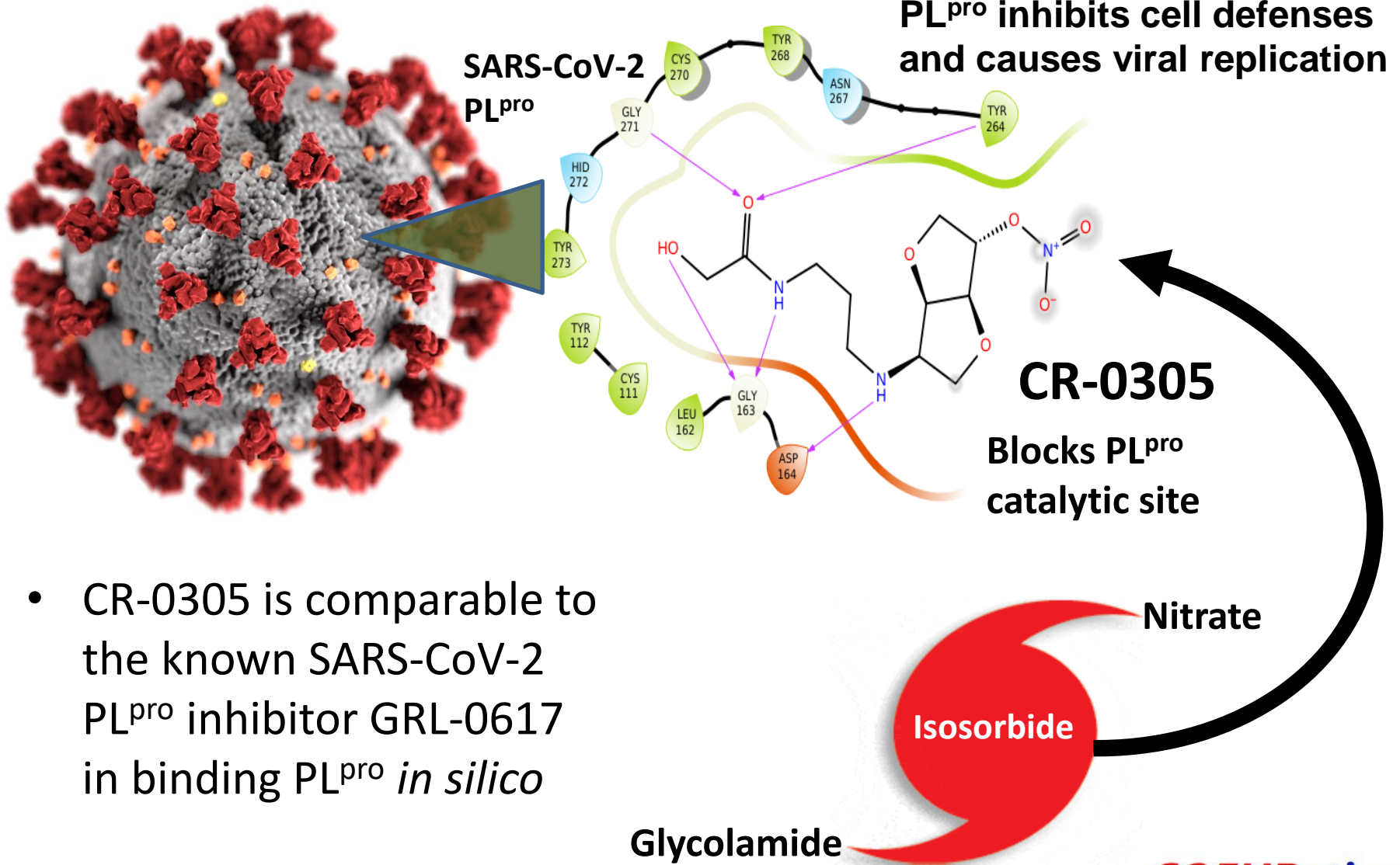
- Nitrate is an NO donor that dilates arteries and may protect against ischemia.
- Glycolamide is a urea analogue that can also facilitate NO formation.
- Targeted delivery of an oral agent that donates NO is desired for both ischemic preconditioning and to restore oxygenation.



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}

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



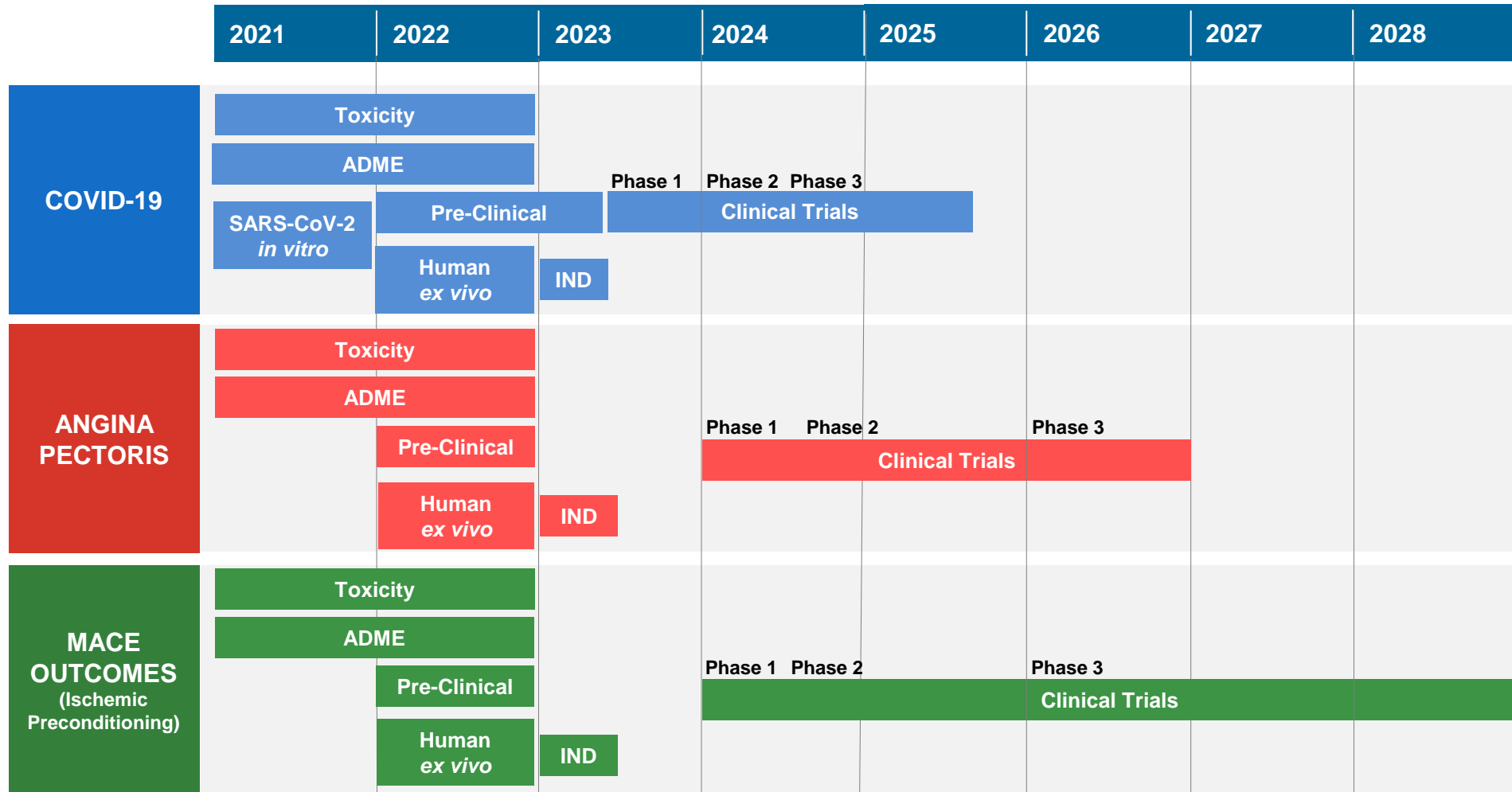
- CR-0305 is comparable to the known SARS-CoV-2 PL^{pro} inhibitor GRL-0617 in binding PL^{pro} *in silico*

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 in collaboration with Robert Davey PhD 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: \$745,000.

Accelerated Development Plan

Contingent on Funding for the Three Proposed Indications for CR-0305



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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