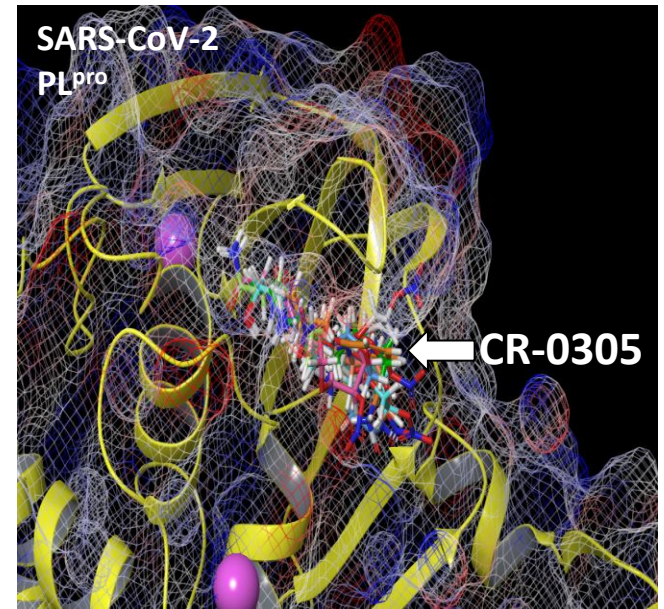


COEURative

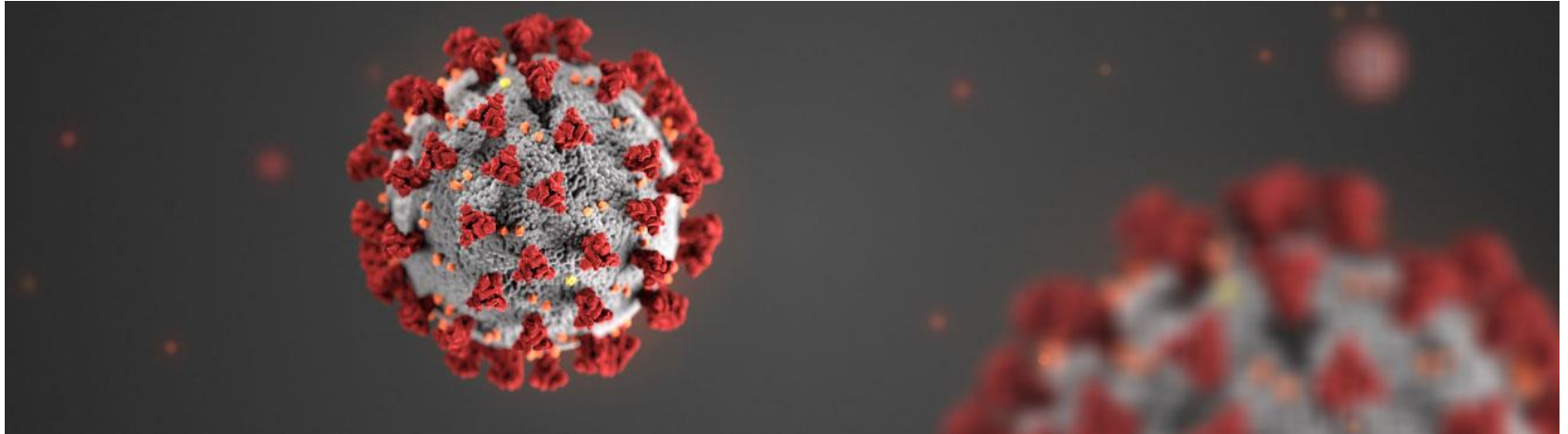
Creating Curative Strategies for Diseases
Associated with Cellular Hypoxia



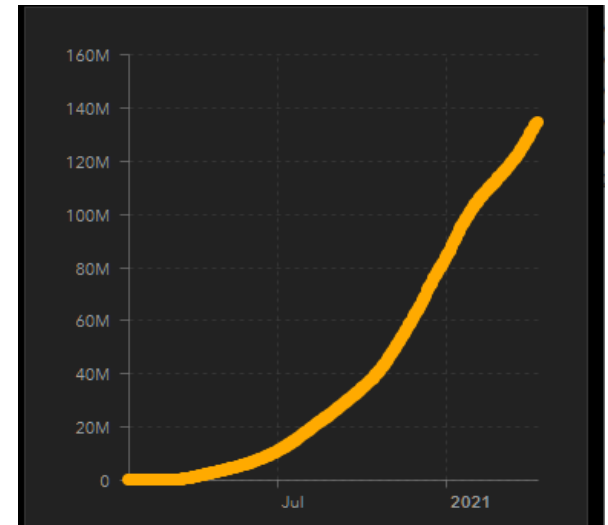
John F. Schmedtje Jr., MD
Founder, President and CEO

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
April 10, 2021

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



- SARS-CoV-2 will not disappear in our lifetime
 - but will evolve.
- 134 million cases and 2.9 million deaths (COVID-19 Worldwide - Johns Hopkins, April 10, 2021)
- Vaccines are coming, and will help, but:
 - data on long term outcomes are not available and
 - broad-based community acceptance is in question.
- Pharmaceutical treatments suboptimal:
 - Remdesivir has a small effect on outcomes.
 - Simply administered oral antivirals needed.



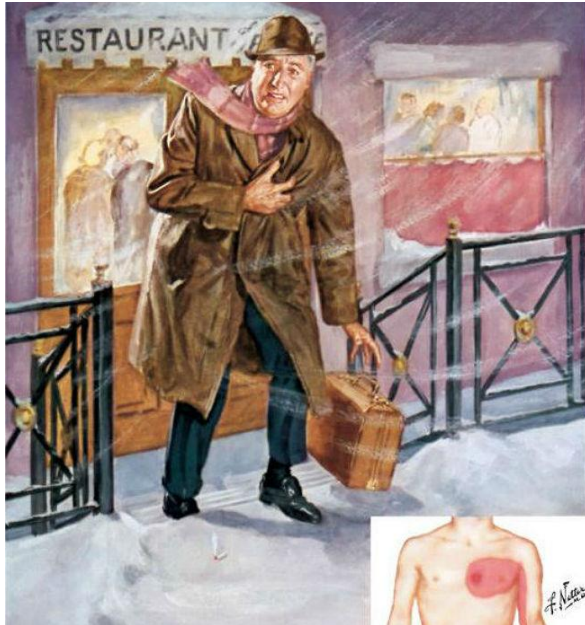
Cumulative Cases

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.

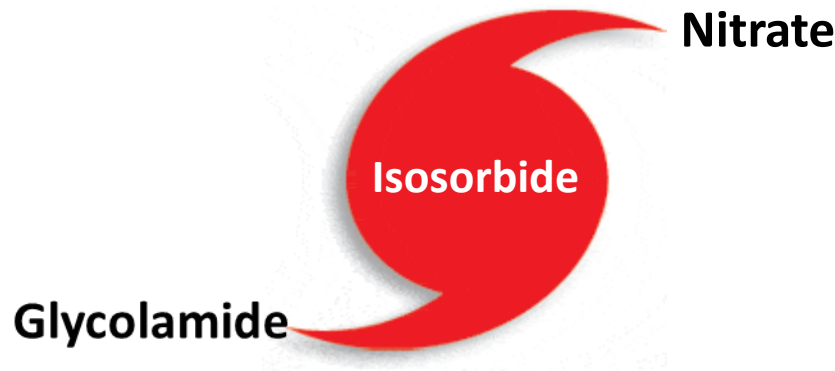
- Nitric Oxide (NO) is donated by NTG (Nitroglycerin) to relax blood vessels.



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

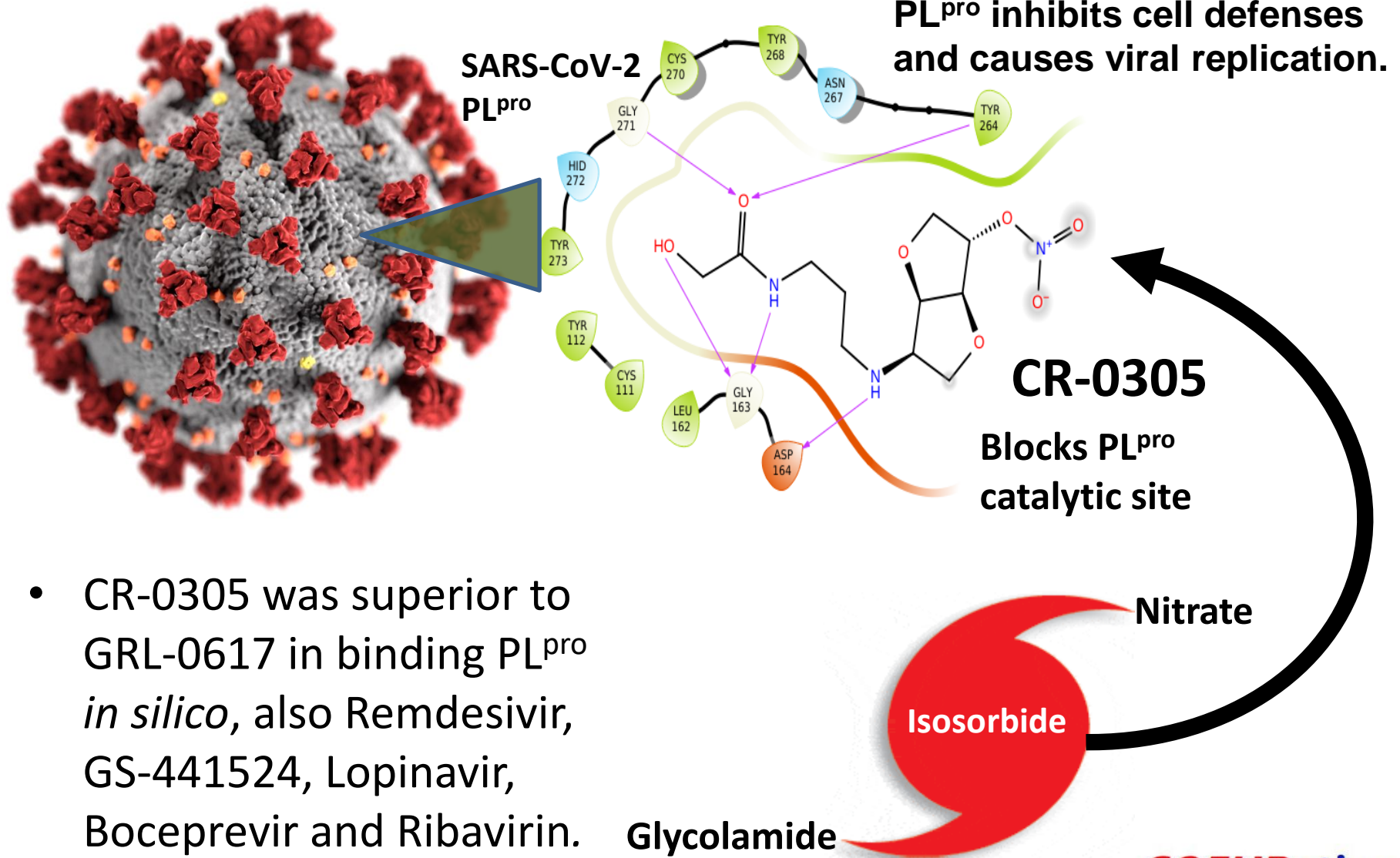
- Nitrate is an NO donor that dilates arteries and may protect against ischemia.
- Glycolamide is a urea analogue that can also facilitate NO formation.
- Targeted delivery of an oral agent that donates NO is desired for both ischemic preconditioning and to restore oxygenation.



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



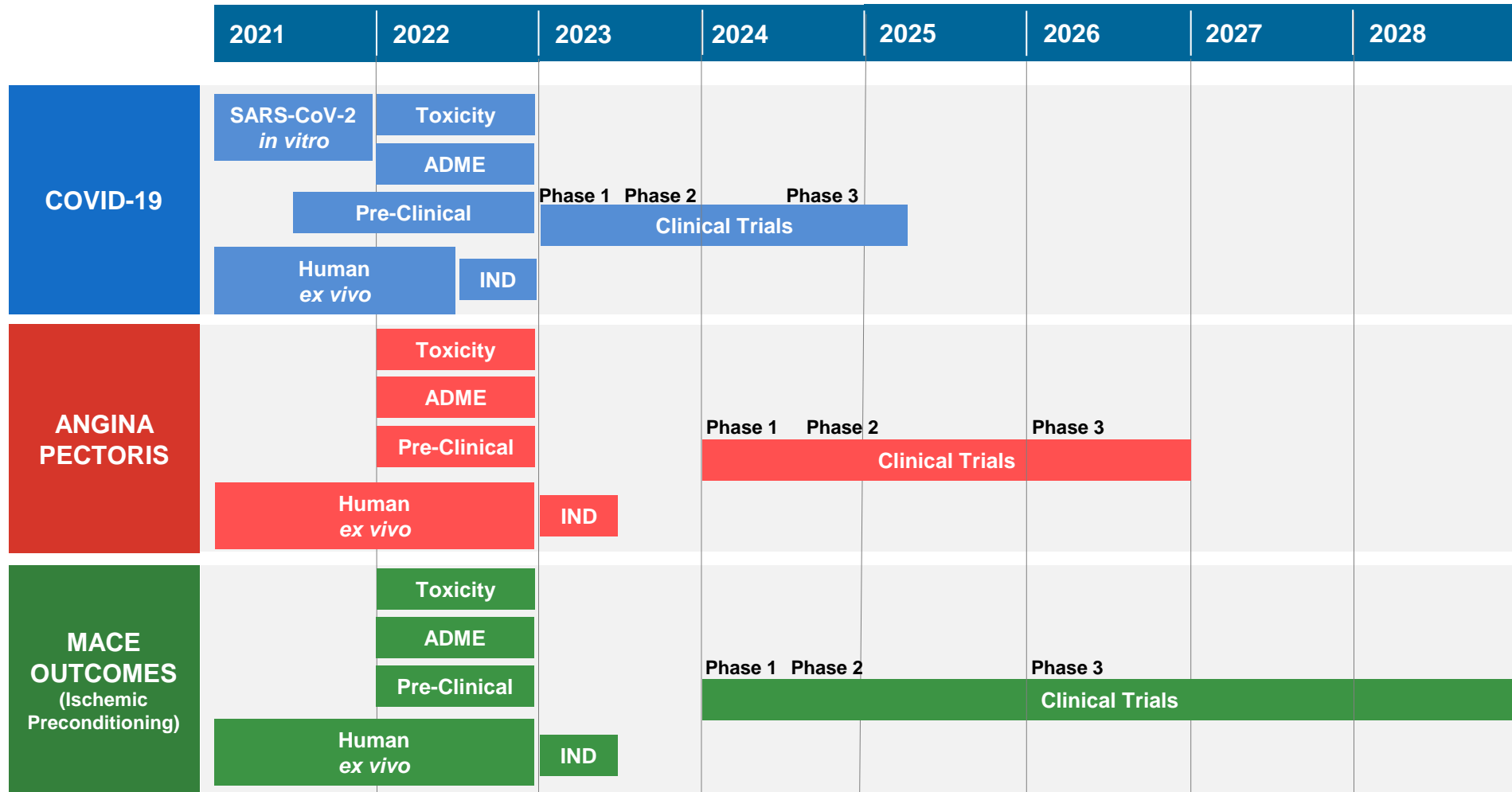
- CR-0305 was superior to GRL-0617 in binding PL^{pro} *in silico*, also Remdesivir, GS-441524, Lopinavir, Boceprevir and Ribavirin.

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 Application PCT/US19/58241 published.
 - International Patent Application PCT/US21/24540 filed.
- \$148,000 of private investment and \$200,000 in series seed funding raised.
- “Novel Experimental Therapeutics For COVID-19 Derived From A Nitric Oxide Donor” presented at American Heart Association Scientific Sessions on November 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 planned.
 - 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.

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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