UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of The Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): August 4, 2020

AERPIO PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-38560**	**61-1547850**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

9987 Carver Road **Cincinnati, OH**	**45242**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code (513) 985-1920

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common stock, $0.0001 par value per share	**ARPO**	**Nasdaq Capital Market**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 or Rule 12b-2 of the Securities Exchange Act of 1934.

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01. Regulation FD Disclosure.

Aerpio Pharmaceuticals, Inc. (the "Company", "we" or "us") is furnishing a corporate presentation, attached as Exhibit 99.2 to this Current Report on Form 8-K, which we intend to use from time to time in meetings with investors and others beginning on August 4, 2020. The corporate presentation will also be available in the investor relations section of the Company's website at http://aerpio.com.

The information in this Item 7.01 and Exhibit 99.2 attached hereto shall not be deemed "filed" for purposes of Section 18 of the Securities and Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall they be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events

On August 4, 2020, we issued a press release announcing the receipt of funding to evaluate subcutaneous razuprotafib in a new randomized, investigational trial for the prevention and treatment of acute respiratory distress syndrome ("ARDS") in adult patients with moderate to severe COVID-19. The trial is part of the MTEC-20-09-COVID-19 Treatment Military Infectious Disease Research Program ("MIDRP"). The Phase 2 clinical trial is expected to be completed in the first quarter of 2021. The Medical Technology Enterprise Consortium ("MTEC"), a non-profit organization primarily funded by the U.S. Army Medical Research and Development Command, will provide up to $5.1 million in funding toward the clinical trial, while we will support the trial with "in-kind" spending in the aggregate amount of $2.8 million.

A copy of the press release is attached hereto as Exhibit 99.1 and incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Press release issued by Aerpio Pharmaceuticals, Inc., on August 4, 2020.
99.2	Aerpio Pharmaceuticals, Inc., corporate presentation.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: August 4, 2020

AERPIO PHARMACEUTICALS, INC.

By: /s/ Joseph Gardner, Ph.D.
Joseph Gardner
President and Founder

Aerpio Pharmaceuticals, Inc. Announces a Second Clinical Trial with Funding from MTEC to Evaluate Razuprotafib for the Prevention and Treatment of ARDS in Patients with Moderate to Severe COVID-19.

CINCINNATI, August 4, 2020 – Aerpio Pharmaceuticals, Inc. (“Aerpio”) (Nasdaq: ARPO) and the U.S. Government operating through the Medical Technology Enterprise Consortium (MTEC) announced today that an agreement has been reached to evaluate razuprotafib in a new randomized, investigational trial for the prevention and treatment of Acute Respiratory Distress Syndrome (ARDS) in adult patients with moderate to severe COVID-19 as part of MTEC-20-09-COVID-19 Treatment Military Infectious Disease Research Program (MIDRP) “Development of Treatments for COVID-19.” MTEC will provide up to $5.1 million in funding toward the clinical trial. Aerpio will support the trial with “in kind” spending in the amount of $2.8 million. MTEC is a 501(c)3 non-profit organization constructed by the U.S. Army Medical Research and Development Command (USAMRDC). The Medical Technology Enterprise Consortium (MTEC) was established as an enterprise partnership including industry and academia to facilitate research and development activities. Protecting U.S. forces from COVID-19 is a key priority for the U.S. military. The partnership between Aerpio and MTEC will provide resources to support a second COVID-19 Phase 2 clinical trial with razuprotafib, a drug candidate being investigated for its potential to prevent and treat the severe respiratory distress observed in COVID-19 patients.

Aerpio Pharmaceuticals is developing a potent and selective small molecule inhibitor of vascular endothelial protein tyrosine phosphatase (VE-PTP), razuprotafib (AKB-9778), that restores Tie2 pathway activation in endothelial cells to stabilize blood vessels during vascular injury and inflammation. Emerging data indicate that SARS-Cov2, the virus that causes COVID-19, may attack vascular endothelium and destabilize blood vessels in multiple organs including the lung, kidneys and heart leading to substantial morbidity and mortality. Based on these findings, Aerpio and a distinguished team of clinical investigators have developed a plan to investigate the therapeutic potential of subcutaneous razuprotafib for the prevention and treatment of ARDS in patients with moderate to severe COVID-19.

Wesley H. Self, MD, MPH Associate Professor and Vice Chair for Research in the Department of Emergency Medicine at Vanderbilt University Medical Center and Aerpio COVID-19 Steering Committee stated “A Tie2 activator that can be administered without an IV to stabilize the pulmonary vasculature would be a breakthrough for reducing the devastating effects of COVID-19 associated pulmonary pathology. This therapeutic could result in fewer COVID-19 patients requiring mechanical ventilation, earlier recovery with decreased time in the hospital and ICU and an overall reduction in morbidity and mortality”.

Jeff Sabados MPP MBA, member of Aerpio's COVID-19 Steering Committee, who served for 20 years in both Active and Reserve Duty in the U.S. Navy, commented "The subcutaneous administration of razuprotafib to activate Tie2 makes this particularly attractive to active duty military personnel around the globe because razuprotafib has the potential to save lives in the next pandemic and return soldiers back to the front lines. I am very proud to be a part of this effort".

About the MTEC Trial

We hypothesize that razuprotafib, a first-in-class Tie2 activating compound, will exhibit an acceptable safety profile and show efficacy for treatment of ARDS in patients with moderate to severe COVID-19 and be a life-saving therapeutic for service members in the field suffering from the devasting respiratory and vascular effects of COVID-19. Aerpio, through the support of MTEC will conduct a Phase 2 clinical trial of subcutaneous razuprotafib for the treatment of patients with moderate to severe COVID-19**.** The Phase 2 trial will be conducted at approximately 10 clinical sites and is expected to be completed in the first quarter of 2021.

About MTEC

The Medical Technology Enterprise Consortium (MTEC) is a 501(c)(3) biomedical technology consortium collaborating under an Other Transaction Agreement (OTA) with the U.S. Army Medical Research and Development Command (USAMRDC) that serves those who serve our nation.

About Razuprotafib (previously AKB-9778)

Razuprotafib binds to and inhibits vascular endothelial protein tyrosine phosphatase (VE-PTP), an important negative regulator of Tie2. Decreased Tie2 activity contributes to vascular instability in many diseases including diabetes. Razuprotafib activates the Tie2 receptor irrespective of extracellular levels of its binding ligands, angiopoietin-1 (agonist) or angiopoietin-2 (antagonist) and may be the most efficient pharmacologic approach to maintain normal Tie2 activation. As seen preclinically, activation of Tie2 by razuprotafib stabilizes vasculature which may have beneficial effects in a variety of disease states, including COVID-19.

About Aerpio Pharmaceuticals

Aerpio Pharmaceuticals, Inc. is a biopharmaceutical company focused on developing compounds that activate Tie2 to treat ocular diseases and diabetic complications. Recently published mouse and human genetic data implicate the Angpt/Tie2 pathway in maintenance of Schlemm's canal, a critical component of the conventional outflow tract. The Company's lead compound, razuprotafib (formerly AKB-9778), a first-in-class small molecule inhibitor of vascular endothelial protein tyrosine phosphatase ("VE-PTP"), is being developed as a potential treatment for open angle glaucoma, and the Company intends to investigate the therapeutic potential of razuprotafib in other indications. The Company is also evaluating development options for ARP-1536, a humanized monoclonal antibody, for its therapeutic potential in the treatment of diabetic vascular complications including nephropathy and diabetic macular edema ("DME"). The Company's third asset is a bispecific antibody that binds both VEGF and VE-PTP which

is designed to inhibit VEGF activation and activate Tie2. This bispecific antibody has the potential to be an improved treatment for wet age-related macular degeneration and DME via intravitreal injection. Finally, the Company has exclusively out-licensed AKB-4924 (now called GB004), a first-in-class small molecule inhibitor of hypoxia-inducible factor-1 (HIF). GB004 is being developed by AKB-4924's exclusive licensor, Gossamer Bio, Inc. (Nasdaq: GOSS). For more information, please visit www.aerpio.com.

Forward Looking Statements

This press release contains forward-looking statements. Statements in this press release that are not purely historical are forward-looking statements. Such forward-looking statements include, among other things, the Company's product candidates, including razuprotafib, ARP-1536 and the bispecific antibody asset, the clinical development plan therefor and the therapeutic potential thereof, the Company's plans and expectations with respect to razuprotafib and the development therefor and therapeutic potential thereof in addressing COVID-19 and the intended benefits from the Company's collaboration with Gossamer Bio for GB004, including the continued development of GB004 and the milestone and royalty payments related to the collaboration. Actual results could differ from those projected in any forward-looking statements due to several risk factors. Such factors include, among others, the continued development of GB004 and maintaining and deriving the intended benefits of the Company's collaboration with Gossamer Bio; ability to continue to develop razuprotafib or other product candidates, including in indications related to COVID-19; the inherent uncertainties associated with the drug development process, including uncertainties in regulatory interactions, the design of planned or future clinical trials, commencing clinical trials and enrollment of patients in clinical trials; obtaining any necessary regulatory clearances in order to commence and conduct planned or future clinical trials; the impact of the ongoing COVID-19 pandemic on the Company's business operations, including research and development efforts and the ability of the Company to commence, conduct and complete its planned clinical activities; and competition in the industry in which the Company operates and overall market conditions; and the additional factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q and our other subsequent filings with the SEC.

These forward-looking statements are made as of the date of this press release, and the Company assumes no obligation to update the forward-looking statements, or to update the reasons why actual results could differ from those projected in the forward-looking statements, except as required by law. Investors should consult all the information set forth herein and should also refer to the risk factor disclosure set forth in the reports and other documents the Company files with the SEC available at www.sec.gov.

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ikoffler@lifesciadvisors.com

Exhibit 99.2

aerpio pharmaceuticals

COVID-19 Program

August 2020

COVID-19 Program: Aerpio Awarded MTEC Grant

Aerpio has been selected to receive funding to support a second clinical trial to prevent and treat respiratory distress in moderate-to-severe COVID-19 patients.

Aerpio announced an agreement to evaluate Aerpio's novel Tie2 activator, razuprotafib, in a new randomized, investigational trial for the prevention and treatment of Acute Respiratory Distress Syndrome (ARDS) in adult patients with moderate to severe COVID-19 as part of MTEC-20-09-COVID-19 Treatment Military Infectious Disease Research Program (MIDRP) "Development of Treatments for COVID-19." MTEC will provide up to $5.1 million in funding toward the clinical trial. Aerpio will support the trial with "in kind" spending in the amount of $2.8 million. Aerpio has manufactured drug product to supply the clinical trial.

This trial, together with the previously announced I-SPY COVID-19 trial, enables the assessment of the potential benefits of vascular stabilization with Razuprotafib in the full spectrum of patients hospitalized with COVID-19.

MTEC is a 501(c)3 non-profit organization primarily funded by the U.S. Army Medical Research and Development Command (USAMRDC).

COVID-19 Program: Aerpio Awarded MTEC Grant

Support from the two Co-Principal Investigators in MTEC Clinical Trial:

Wesley H. Self, MD, MPH Associate Professor and Vice Chair for Research in the Department of Emergency Medicine at Vanderbilt University Medical Center and Aerpio COVID-19 Steering Committee stated "A Tie2 activator that can be administered without an IV to stabilize the pulmonary vasculature would be a breakthrough for reducing the devasting effects of COVID-19 associated pulmonary pathology. This therapeutic could result in fewer COVID-19 patients requiring mechanical ventilation, earlier recovery with decreased time in the hospital and ICU and an overall reduction in morbidity and mortality".

Samir Parikh, MD, Professor of Medicine, Harvard Medical School, Director, Center for Vascular Biology Research, Department of Medicine Beth Israel Deaconess Medical Center, and a member of Aerpio's COVID-19 Steering Committee.

COVID-19 Program: Aerpio Invited into I-SPY Network

Recall on May 27, 2020 the I-SPY Network (Quantum Leap Health Collaborative, QLHC) invited Aerpio into their platform trial to treat patients with ARDS due to critical COVID-19, including those on ventilator support. The I-SPY agreement requires a $1.5 million spend from Aerpio.

I-SPY (Quantum Leap Health Collaborative, QLHC) I-SPY network supports the clinical sites and acts as the clinical CRO for their sites with the target to treat 120 severe COVID-19 patients. Aerpio supplies drug and provides regulatory support for the trial. Drug supply already produced to support a fast start up of the trial (NCT04488081).

I-SPY COVID-19 (I-SPY2) Leadership: Michael Matthay, MD, Professor of Medicine UCSF; Carolyn Calfee, MD, Professor of Medicine and Critical Care UCSF; Nuala Meyer, MD Associate Professor of Medicine, University of Pennsylvania; and Laura Esserman, MD, Co-Principal Investigator of I-SPY2, Member, QLHC Board of Directors

Aerpio (razuprotafib = AKB-9778) was one of four drugs selected to be included in the I-SPY platform trial and is the highest priority drug on their platform (dozens of programs were evaluated)

COVID Grants: Background on MTEC and I-SPY (QLHC) Organizations

Medical Technology Enterprise Organization – MTEC

- Funded primarily by US Army Medical Research and Development Command (USAMRDC)
- From Website "OUR MISSION: To be the partner of choice for private industry, academic institutions, government agencies, and other research organizations seeking to accelerate the development of medical solutions that prevent and treat injuries and restore America's military and veterans to full health."

I-SPY – Quantum Leap Healthcare Collaborative (QLHC)

- Originally formed as collaborative network to run rapid trials using adaptive design in oncology to optimize drug combinations and new entities for cancer
- Initiated collaborative network to run trials in COVID-19 patients on March 17th, 2020

I-SPY COVID-19 (I-SPY2) Leadership: Michael Matthay, MD, Professor of Medicine UCSF; Carolyn Calfee, MD, Professor of Medicine and Critical Care UCSF; Nuala Meyer, MD Associate Professor of Medicine, University of Pennsylvania; and Laura Esserman, MD, Co-Principal Investigator of I-SPY2, Member, QLHC Board of Directors

Have selected 4 drugs to include in COVID Network Trial with Aerpio's drug as top priority

"Aerpio's drug is the one that most excites the investigators." Dr. Michael Matthay Professor of Pulmonary and Critical Care Medicine, UCSF and ISPY investigator

Aerpio COVID-19 Steering Committee

Strong Support from Highly Regarded Steering Team; received significant input on trial design and introductions to I-SPY team

Member	Affiliation
Dr. Gordon Bernard	Professor of Medicine, Melinda Owen Bass Chair in Medicine, Associate Vice Chancellor for Research, Vanderbilt University Medical Center
Dr. Chris Kontos	Professor of Medicine, Professor of Pharmacology and Cancer Biology, Duke University
Dr. Michael Lotze	Professor of Surgery, Immunology and Bioengineering, Vice Chair of Research, Department of Surgery, University of Pittsburgh
Dr. John Marshall	Professor of Surgery, St. Michael's Hospital, University of Toronto
Dr. Samir Parikh	Professor of Medicine, Director, Center for Vascular Biology Research Associate Vice Chair for Research, Department of Medicine Beth Israel Deaconess Medical Center, Harvard Medical School
Dr. Marc Pritzker	Professor of Medicine, Surgery and Biomedical Innovation, Cardiovascular Division, University of Minnesota
Dr. Wesley Self	Associate Professor of Emergency Medicine, Vanderbilt University Medical Center

Why Razuprotafib?: Restoring Tie2 Activation Enhances Endothelial Function and Vascular Stability to Improve Outcomes in COVID-19

COVID-19: the vasculature unleashed

Laure-Anne Teuwen[1,2,3], Vincent Geldhof[1], Alessandra Pasut[1] and Peter Carmeliet[1,4]

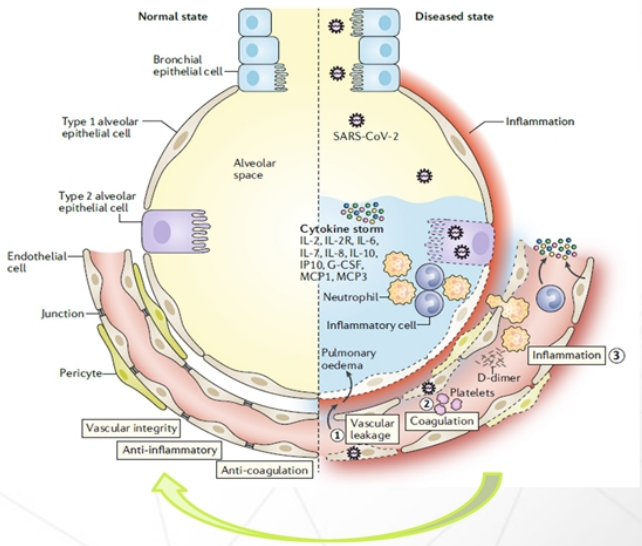
On the basis of emerging evidence from patients with COVID-19, we postulate that endothelial cells are essential contributors to the initiation and propagation of severe COVID-19. Here, we discuss current insights into the link between endothelial cells, viral infection and inflammatory changes and propose novel therapeutic strategies.

Teuwen *et al. Nat Rev Immunol* (2020). https://doi.org/10.1038/s41577-020-0343-0

Tie2 Activation with Razuprotafib could Improve Outcomes in COVID-19 by Reducing:

Inflammation
Vascular leakage
Endothelial cell dysfunction and loss
In situ thrombosis
Pulmonary vascular resistance
V/Q mismatch
"Angiofibrosis"

all of which could improve the physiology and outcomes of patients with COVID-19.



Razuprotafib (AKB-9778)

COVID-19 Program: Summary of Science Supporting Hypothesis (detailed slides in next section)

Preclinical:
Multiple animal models performed by collaborators show that Tie2 activation stabilizes blood vessels to improve endothelial function, reduce vascular leakage and rescue animals from "cytokine storm" associated with ARDS and sepsis

Both Tie2 and VE-PTP highly expressed in lung

Tie2 activation improves endothelial viability and function via the AKT pathway; enhances stability of endothelial junctions and reduces vascular leakage via rac activation; reduces inflammation via inhibition of NF kappa B, a known pro-inflammatory mediator

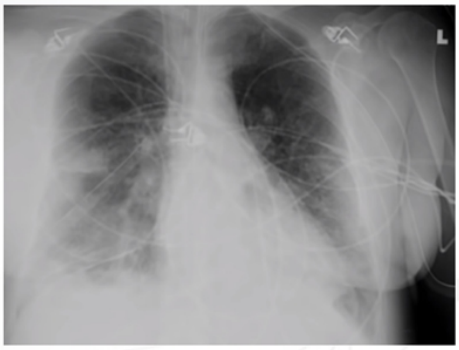
Clinical:
Aerpio clinical data demonstrates AKT/eNOS pathway activation (via acute blood pressure reduction) which supports vascular stabilizing, antithrombotic and anti-inflammatory effect

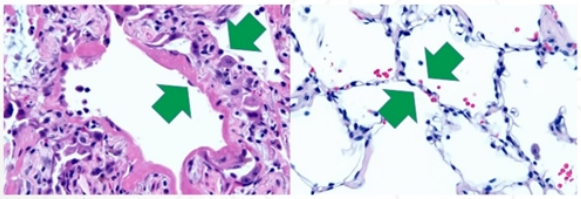
Aerpio clinical data demonstrates lowering of C-reactive protein (CRP) a marker of vascular inflammation. COVID-19 patients have dramatically high levels of CRP

Several recent articles indicate that COVID-19 infection produces a "vasculitis" that results in profound leak of fluid and inflammatory cells into the lung and drives thrombotic and thromboembolic complications


aerpio
pharmaceuticals
COVID-19 Program: Scientific Rationale
August 2020

COVID-19 is a Rapidly Progressive Viral Infection that Quickly Leads to Respiratory Failure





~30% progress to ARDS within 2 days of admission

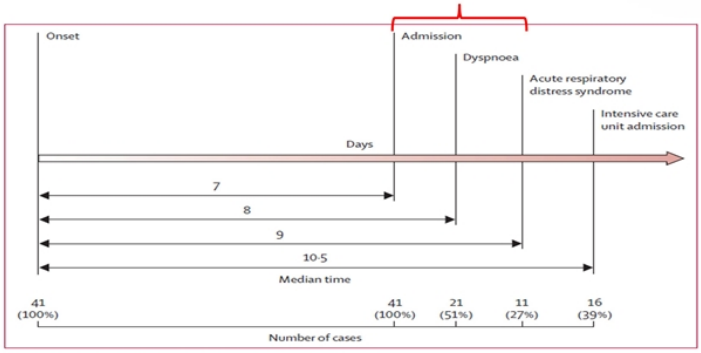


Figure 2: **Timeline of 2019-nCoV cases after onset of illness**

- Rapid progression to respiratory failure leads to mortality and overwhelms the healthcare system (ICU and ventilator capacity)
- What is needed is an effective host targeted intervention to ameliorate progression of the pulmonary pathology

COVID-19 : A Deadly Pandemic with Limited Treatment Options

NIH | COVID-19 Treatment Guidelines

- Remdesivir and dexamethasone now recommended for certain subsets of hospitalized COVID-19 patients
- Older antivirals and hydroxychloroquine have failed
- Although extensively studied, other anti-inflammatory agents (biologicals and small molecules) are not recommended except in clinical trials
- Despite the availability of remdesivir and dexamethasone, morbidity and mortality among hospitalized patients with COVID-19 remains unacceptably high

➢ Emerging data indicate blood vascular endothelium is a target for SARS-CoV-2 and could play an important role in COVID-19 disease progression

➢ Based on these data, a vascular stabilizing agent could be an important addition to the COVID-19 treatment regimen

Key Updates to the Guidelines *Updated July 17th, 2020*

Remdesivir

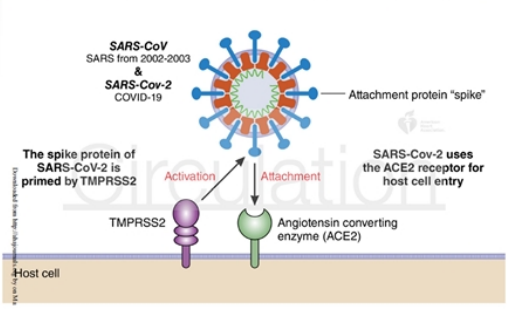
In situations where remdesivir supplies are limited, the COVID-19 Treatment Guidelines Panel (the Panel) recommends prioritizing **remdesivir** for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated or on extracorporeal membrane oxygenation **(BI)**. The overall recommendations for the use of remdesivir are being revised and will be updated soon.

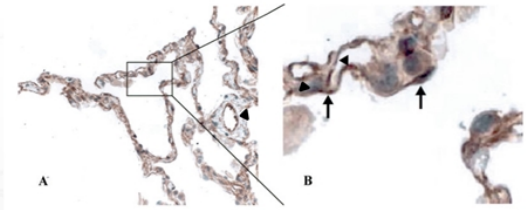
Corticosteroids (Including Dexamethasone)

The Corticosteroids (Including Dexamethasone) section is a new subsection of Immunomodulators Under Evaluation for Treatment of COVID-19. This new section is based on the Recommendations for Dexamethasone in Patients with COVID-19 section that was released on June 25, 2020. The Panel continues to recommend the use of **dexamethasone** in patients who are mechanically ventilated **(AI)** and in patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**. The new Corticosteroids (Including Dexamethasone) section also discusses the clinical data on the use of other corticosteroids in patients with COVID-19, the potential adverse effects of corticosteroids, other considerations when using corticosteroids, and recommendations for the use of dexamethasone in pregnant patients.

https://www.covid19treatmentguidelines.nih.gov/whats-new/

The SARS-CoV-2 Receptor, ACE2, is Expressed on Pulmonary Epithelium **and Endothelium** Indicating both are Disease Targets





ACE2 expression in normal lung tissue: overview (A) and higher magnification (B). Positive staining for ACE2 is clearly present on alveolar epithelial cells (arrow) and microvessel/capillary endothelium (arrow-head).

The pulmonary endothelium in acute respiratory distress syndrome: insights and therapeutic opportunities
Fraser R Millar, Charlotte Summers, Mark J Griffiths, Mark R Toshner and Alastair G Proudfoot
Thorax 2016;71:462–473. doi:10.1136/thoraxjnl-2015-207461

"The pulmonary endothelium is increasingly seen as pivotal in both the progression and the resolution of ARDS and is therefore primed as a therapeutic target."

Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis
I Hamming, W Timens, MLC Bulthuis, AT Lely, GJ Navis and H van Goor
J Pathol 2004; 203: 631–637

"ACE2 was present in **arterial and venous endothelial cells** and arterial smooth muscle cells in all organs studied."

Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality
Robert O. Bonow, MD, MS; Gregg C. Fonarow, MD; Patrick T. O'Gara, MD; Clyde W. Yancy, MD, MSc
JAMA Cardiology Published online March 27, 2020

"It is noteworthy that the articles from China by Shi et al,[10] Guo et al,[11] and Yang and Zin[12] address the unique marked affinity of SARS-CoV-2 for the host angiotensin-converting enzyme 2 receptor, which has been shown previously for other coronaviruses,[13] raising the possibility of direct viral infection **of vascular endothelium** and myocardium."

COVID-19 can Infect and Replicate in Human Capillary Organoids

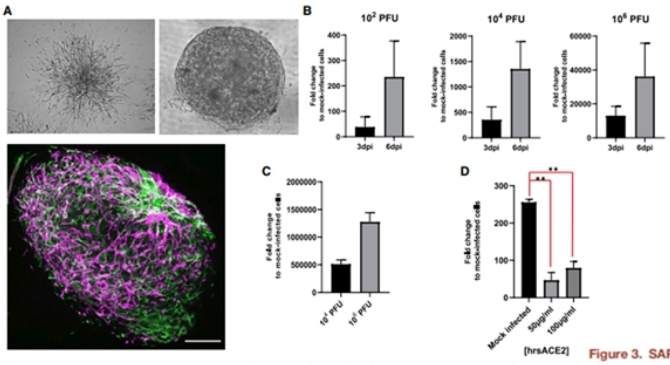


Figure 3. SARS-CoV-2 Infections of Blood Vessels Organoids

(A) Representative images of vascular capillary organoids using light microscopy (magnifications ×10) (upper panels) and immunostaining of blood vessel organoids using anti-CD31 to detect endothelial cells and anti-PDGFRβ to detect pericytes. DAPI (blue) was used to visualize nuclei. Scale bars, 500 μm and 50 μm (inset).

(B) Recovery of viral RNA from blood vessel organoids at day 3 and 6 post-infection (dpi) with SARS-CoV-2, demonstrating that the virus can infect the vascular organoids. Data are represented as mean ± SD.

(C) Determination of progeny virus. Supernatants of SARS-CoV-2 infected blood vessel organoids were collected 6 dpi and then used to infect Vero E6 cells. After 48 h, Vero E6 cells were washed and viral RNA assessed by qRT-PCR. The data show that infected blood vessel organoids can produce progeny SARS-CoV-2 viruses, depending on the initial level of infection. Data are represented as mean ± SD.

(D) Effect of hrsACE2 on SARS-CoV-2 infections of blood vessel organoids. Organoids were infected with a mix of 10^6 infectious viral particles and hrsACE2 for 1 h. 3 dpi, levels of viral RNA were assessed by qRT-PCR. hrsACE2 significantly decreased the level of SARS-CoV-2 infections in the vascular organoids. Data are represented as mean ± SD (Student's t test: $^{**}p < 0.01$).

Monteil et al. Cell Correspondence https://doi.org/10.1016/j.cell.2020.04.004

Endothelial Cell Infection and Endothelialitis in COVID-19

Varga et al. The Lancet April 17, 2020 https://doi.org/10.1016/ S0140-6736(20)30937-5

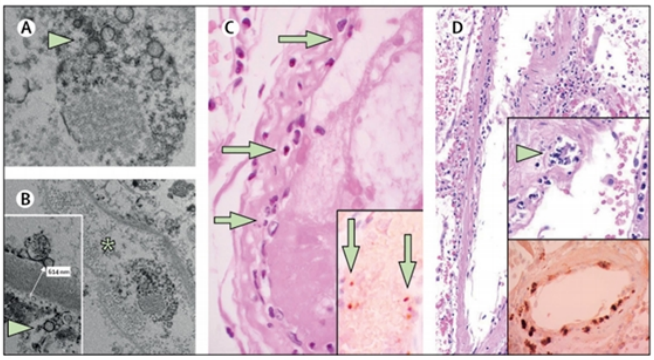


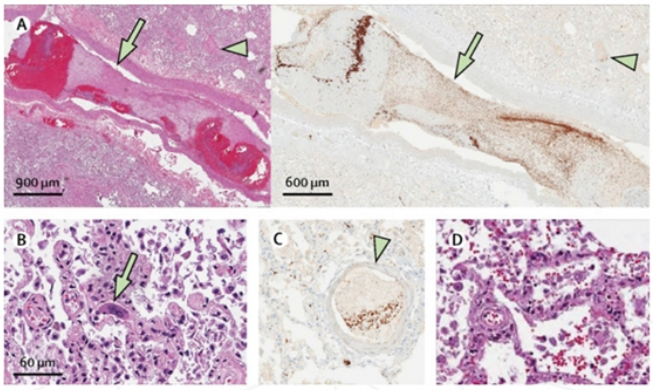
***Figure*: Pathology of endothelial cell dysfunction in COVID-19**
(A, B) Electron microscopy of kidney tissue shows viral inclusion bodies in a peritubular space and viral particles in endothelial cells of the glomerular capillary loops. Aggregates of viral particles (arrow) appear with dense circular surface and lucid centre. The asterisk in panel B marks peritubular space consistent with capillary containing viral particles. The inset in panel B shows the glomerular basement membrane with endothelial cell and a viral particle (arrow; about 150 nm in diameter). (C) Small bowel resection specimen of patient 3, stained with haematoxylin and eosin. Arrows point to dominant mononuclear cell infiltrates within the intima along the lumen of many vessels. The inset of panel C shows an immunohistochemical staining of caspase 3 in small bowel specimens from serial section of tissue described in panel D. Staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections, indicating that apoptosis is induced in a substantial proportion of these cells. (D) Post-mortem lung specimen stained with haematoxylin and eosin showed thickened lung septa, including a large arterial vessel with mononuclear and neutrophilic infiltration (arrow in upper inset). The lower inset shows an immunohistochemical staining of caspase 3 on the same lung specimen; these staining patterns were consistent with apoptosis of endothelial cells and mononuclear cells observed in the haematoxylin-eosin-stained sections. COVID-19=coronavirus disease 2019.

"Our findings show the presence of viral elements within endothelial cells and an accumulation of inflammatory cells, with evidence of endothelial and inflammatory cell death. These findings suggest that SARS-CoV-2 infection facilitates the induction of endotheliitis in several organs as a direct consequence of viral involvement (as noted with presence of viral bodies) and of the host inflammatory response. In addition, induction of apoptosis and pyroptosis might have an important role in endothelial cell injury in patients with COVID-19. COVID-19- endotheliitis could explain the systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19. This hypothesis provides a rationale for therapies to stabilize the endothelium while tackling viral replication, particularly with anti-inflammatory anti-cytokine drugs, ACE inhibitors, and statins. This strategy could be particularly relevant for vulnerable patients with pre-existing endothelial dysfunction, which is associated with male sex, smoking, hypertension, diabetes, obesity, and established cardiovascular disease, all of which are associated with adverse outcomes in COVID-19."

Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans

Fox et al. The Lancet Respiratory Medicine May 27, 2020, DOI:https://doi.org/10.1016/S2213-2600(20)30243-5

"We believe that effective therapy for this patient demographic—and probably patients with severe infection across demographics—should target not only the viral pathogen, but also the thrombotic and microangiopathic effects of the virus, and possibly a maladaptive immune response to viral infection."

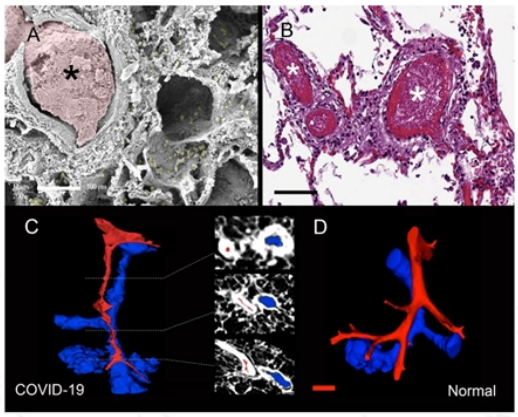


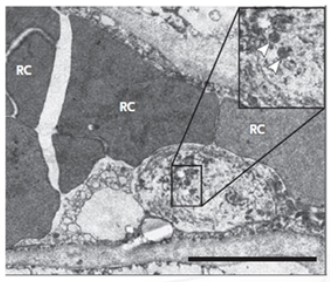
Pulmonary thrombi and microangiopathy (A) Thrombus in a small pulmonary artery (green arrow), with small thrombus seen in adjacent pulmonary venule (green arrowhead), with H&E present on the left, and CD61 immunostain highlighting platelets within the thrombi on the right. (B) Many megakaryocytes were present within the small vessels and alveolar capillaries (green arrow). (C) CD61 immunostain highlighting additional fibrin and platelet thrombus shown in a small vessel, with megakaryocyte stained below (green arrowhead). Von Willebrand Factor immunostain additionally highlighted these vessels (appendix p 8). (D) Small, perivascular aggregates of lymphocytes. Also present were small lymphocytic aggregates surrounding airways, which were positive for CD4 immunostain, with only scattered CD8 positive cells present (appendix p 7).

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Ackermann et al. N Engl J Med 2020; 383:120-128, July 9, 2020, DOI: 10.1056/NEJMoa2015432

The lungs from patients with Covid-19 showed distinctive vascular features including severe endothelial injury associated with intracellular virus and disrupted cell membranes (right panel) and widespread thrombosis with microangiopathy (left panel). Alveolar capillary microthrombi were 9 times as prevalent in patients with Covid-19 as in patients with influenza (P<0.001).





"The presence of SARS-CoV-2 virus within the endothelial cells, a finding consistent with other studies, suggests that direct viral effects as well as perivascular inflammation may contribute to the endothelial injury."

Patient Characteristics Associated with Endothelial Dysfunction and Vascular Injury are Risk Factors for ARDS and Mortality

Table 4. Bivariate Cox Regression of Factors Associated With ARDS Development or Progression From ARDS to Death

	ARDS		Death	
Patient characteristics and findings	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Clinical characteristics				
Age (≥65 vs <65), y	3.26 (2.08-5.11)	<.001	6.17 (3.26-11.67)	<.001
Gender (male vs female)	1.47 (0.92-2.36)	.11	0.56 (0.30-1.05)	.07
Highest patient temperature (≥39 °C vs <39 °C)	1.77 (1.11-2.84)	.02	0.41 (0.21-0.82)	.01
Comorbidities				
Hypertension (yes vs no)	1.82 (1.13-2.95)	.01	1.70 (0.92-3.14)	.09
Diabetes (yes vs no)	2.34 (1.35-4.05)	.002	1.58 (0.80-3.13)	.19
Laboratory findings				
Infection-related indices				
hs-CRP, mg/L (>5 vs ≤5)	4.81 (1.52-15.27)	.008	NA	NA
IL-6, pg/L	1.02 (1.00-1.05)	.09	1.03 (1.01-1.05)	.01
ESR, mm/h	1.01 (1.00-1.02)	.19	1.01 (0.99-1.02)	.32
Serum ferritin, ng/mL (>300 vs ≤300)	3.53 (1.52-8.16)	.003	5.28 (0.72-38.48)	.10
Coagulation function				
PT, s	1.56 (1.32-1.83)	<.001	1.08 (0.84-1.38)	.54
APTT, s	0.97 (0.94-1.01)	.13	0.96 (0.91-1.00)	.06
D-dimer, μg/mL	1.03 (1.01-1.04)	<.001	1.02 (1.01-1.04)	.002

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China
Chaomin Wu, MD; Xiaoyan Chen, MD; Yanping Cai, MD; et al
JAMA Intern Med. Published online March 13, 2020.
doi:10.1001/jamainternmed.2020.0994

"Of 201 patients, the median age was 51 years (interquartile range, 43-60 years), and 128 (63.7%) patients were men. Eighty-four patients (41.8%) developed ARDS, and of those 84 patients, 44 (52.4%) died."

Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic
Elissa Driggin, et al.
JACC https://doi.org/10.1016/j.jacc.2020.03.031 JAC 27204

"Increased case-fatality rates in the previously referenced analysis of 44,672 confirmed COVID-19 cases from Wuhan, China were noted in patients with CVD (10.5%), diabetes (7.3%), hypertension (6.0%), all notably higher than the overall case-fatality rate of 2.3%."

Active Tie2 is Essential for Maintaining Endothelial Function and Vascular Stability

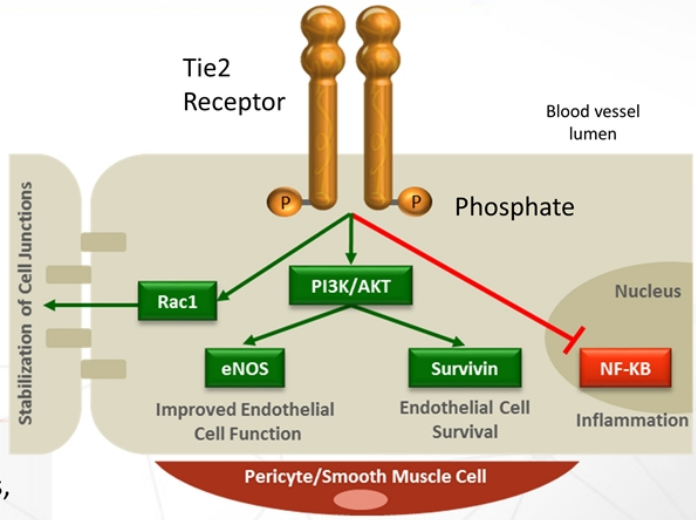
Tie2 is a transmembrane receptor found on endothelial cells, the foundation for vascular stability

Tie2 activity…

- Enhances endothelial cell function and viability
- Maintains integrity of endothelial cell junctions
- Inhibits vascular inflammation and thrombosis

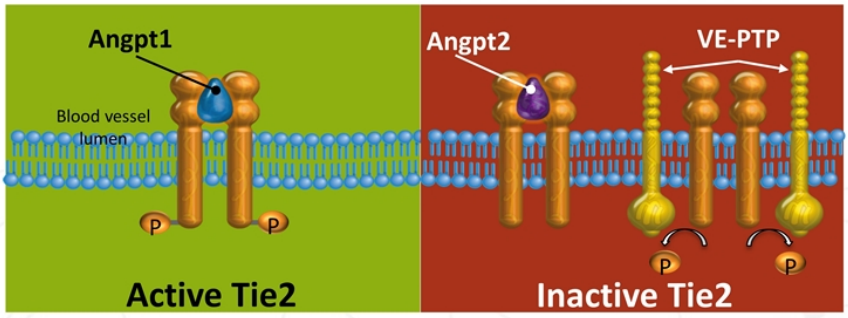
Inactive Tie2 = Vascular Destabilization

- Promotes endothelial cell dysfunction and apoptosis, vascular leakage and inflammation, thrombogenesis and fibrosis
- Enables pathologic neovascularization



Reduced Tie2 Activation Could Contribute to the Development of Respiratory Failure and Vascular Complications and in COVID-19

- Angpt1 acts as a full agonist activator of Tie2, while Angpt2 is a weak partial agonist (context-dependent Tie2 inhibitor)
- There are increased circulating Angpt2 levels in ARDS and sepsis that correlate with disease severity and mortality
- VE-PTP is a negative regulator of Tie2 that is also upregulated in stressed endothelium (diabetes, hypertension and hypoxia) creating an Angpt1 resistant state that further limits Tie2 activation
- Reduced Tie2 activation leads to endothelial dysfunction, vascular leak, inflammation and thrombosis, characteristic of COVID-19 and ARDS

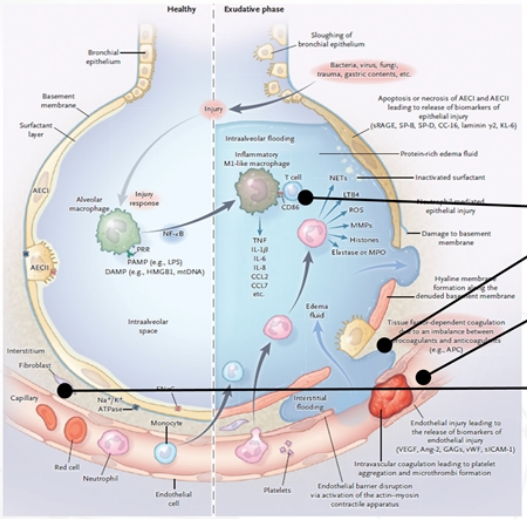


Angpt1 responsive, Stable normal vasculature

Angpt1 resistant, Destabilized COVID-19 vasculature

Angpt-1 – Angiopoietin 1; Angpt-2 – Angiopoietin 2; VE-PTP – Vascular endothelial protein tyrosine phosphatase

Hypothesis: Tie2 Activation Stabilizes Blood Vessels to Improve Outcomes in COVID-19



Tie2 Activation Impacts Key Components of COVID-19 Pathology by Reducing:

- Inflammation
- Vascular leakage
- Endothelial cell dysfunction and loss
- In situ thrombosis
- Pulmonary vascular resistance
- V/Q mismatch
- "Angiofibrosis"

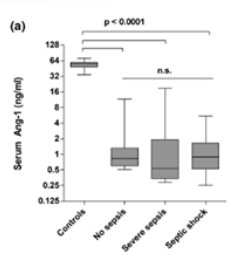
all of which could improve the physiology and outcomes of patients with COVID-19.

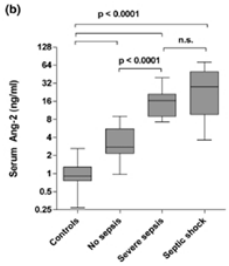
Table 1: Disparate Models of Lung Injury Improve with Tie2 Activation*
Biological/Chemical Warfare
Phosgene
Systemic anthrax lethal toxin
Common Infections/Inflammation
Intratracheal LPS
Parenteral LPS
Abdominal sepsis from CLP
IL-6
Others
Hyperoxic lung injury
Serotonin pulmonary hypertension
Monocrotaline

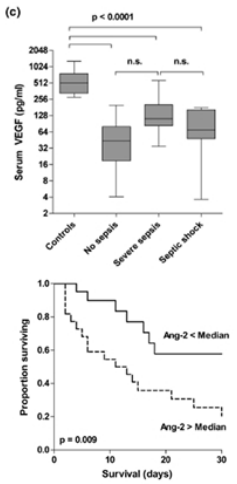
* References available on request

Figure 1: ARDS pathophysiology and Tie2. Left schema from B. Taylor Thompson, et al. NEJM 2017. Tie2 activation exerts multiple salutary effects.

Circulating Angpt2, a Context-Dependent Tie2 Antagonist, Correlates with Disease Severity and Predicts Mortality in Sepsis and ARDS







Kaplan-Meier curves of survival stratified to Angiopoietin (Ang) 2.
(less versus greater than median; Log rank test p = 0.009).

43 patients:
12 severe sepsis
17 septic shock
14 critically ill (not septic)

29 age and gender matched HVs

Kumpers et al. Critical Care 12:R147, 2008

Angiopoietin-2 Levels as Predictors of Outcome in Mechanically Ventilated Patients with Acute Respiratory Distress Syndrome.
Tsangaris et al. *Disease Markers*, Vol 2017
https://doi.org/10.1155/2017/6758721

Plasma Angiopoietin-2 Predicts the Onset of Acute Lung Injury in Critically Ill Patients.
Agrawal et al. *Am J Respir Crit Care Med,* Vol 187: 736–742, 2013

Plasma angiopoietin-2 in clinical acute lung injury: Prognostic and pathogenetic significance.
Calfee et al. *Crit Care Med,* 40(6): 1731–1737, 2012
doi:10.1097/CCM.0b013e3182451c87

Lilly Advances Angpt2 Neutralizing Antibody (LY3127804)

BioSpace

Eli Lilly to Begin Testing RA Drug Olumiant and an Anti-Ang2 Drug in COVID-19 Patients

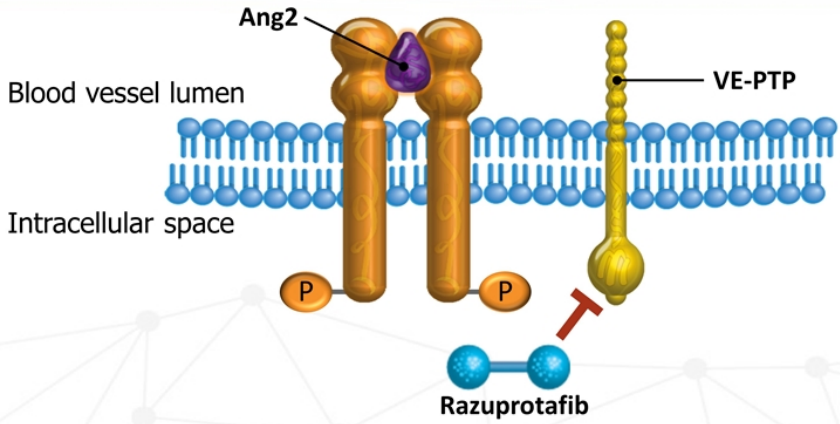
Eli Lilly is also advancing LY3127804, an investigational selective monoclonal antibody against Angiopoietin 2 (Ang2), to Phase II testing in pneumonia patients hospitalized with COVID-19 who are at a higher risk of progressing to acute respiratory distress syndrome (ARDS). Ang2 is known to be elevated in ARDS patients and Lilly will test whether inhibiting the effects of Ang2 with a monoclonal antibody can reduce the progression to ARDS or the need for mechanical ventilation in COVID-19 patients, Eli Lilly said. The study with LY3127804 is expected to begin later this month at multiple sites in the United States (NCT04342897).

https://clinicaltrials.gov/ct2/show/NCT04342897?term=LY3127804&cond=COVID&draw=2&rank=1

While this seems like a reasonable approach, neutralizing Angpt2:

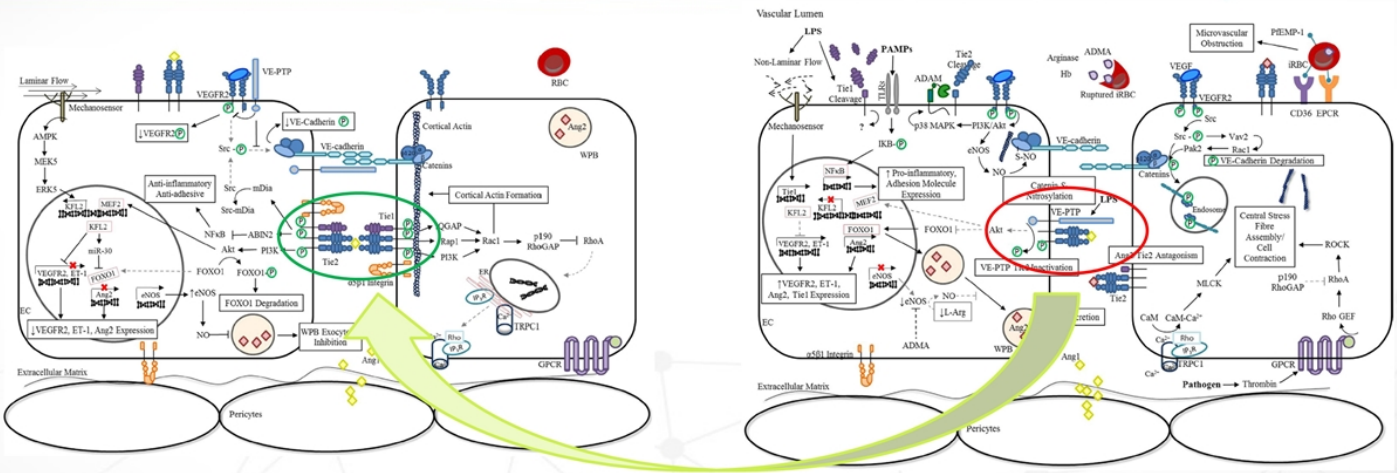
- Requires presence of Angpt1 to restore Tie2 activation (Regula et al. *EMBO Mol Med* 8:1265-1288, 2016)
- Does not deal with Angpt1 resistance due to increased expression of VE-PTP (Shen et al. *JCI* 124:4564-4576, 2014; Souma et al. *PNAS* 115:1298-1303, 2018; Carota et al. *J Exp Med* 216:936-949, 2019)
- Could be counter productive as Angpt2 may maintain low level of Tie2/Akt activation required for viability of stressed endothelium (Daly et al. *PNAS* 103:15491-15496, 2006)

Targeting VE-PTP: The most Effective and Efficient Pharmacologic Approach to Tie2 Activation



- VE-PTP dephosphorylates Tie2 to render it inactive and is the most downstream negative regulator of the Tie2 pathway
- Inhibiting the catalytic domain of VE-PTP with razuprotafib restores Tie2 activation in the absence of Angpt1 or Angpt2 and enhances the agonist properties of both ligands
- Inhibiting VE-PTP with razuprotafib restores Tie2 activation and Angpt1 sensitivity in hypoxic endothelial cells
- **Targeting VE-PTP is the most effective and efficient pharmacologic approach to restoring Tie2 activation**

Tie2 Signaling in Health (left) and in COVID-19/ARDS (right)



Razuprotafib (AKB-9778)

- VE-PTP, the molecular target of Razuprotafib, is the most downstream negative regulator of Tie2
- Razuprotafib inhibits VE-PTP restoring Tie2 activation and vascular stability to improve outcomes in COVID-19/ARDS

Leligdowicz et al. Frontiers in Immunol, 2018 doi: 10.3389/fimmu.2018.00838

Razuprotafib (AKB-9778) Preclinical Summary

- Razuprotafib is a highly optimized, small molecule VE-PTP inhibitor that activates Tie2, to enhance endothelial function and stabilize blood vessels, including pulmonary, renal and cerebral vasculature.
- VE-PTP is upregulated in “stressed” endothelium in conditions relevant to COVID-19 including diabetes, hypertension and hypoxia.
- Razuprotafib reduces LPS (lipopolysaccharide/endotoxin) mediated vascular leakage and leukocyte transmigration (neutrophil and lymphocyte) in the lung, two key components of COVID-19 pulmonary pathology that contribute to respiratory failure.
- Razuprotafib reduces lung toxicity and improved survival in a mouse model of IL2-induced cytokine storm possibly relevant to cytokine storm that is associated with poor outcomes in COVID-19.
- VE-PTP inhibition improved outcomes in LPS-induced acute renal injury and cerebral ischemia indicating potential benefits of restoring Tie2 activation in crucial vascular beds outside the lung.
- Chronic (6-9 months) GLP toxicity studies in three species (monkey, dog and rat) at many fold over clinical exposures have been well tolerated with no dose-limiting adverse effects identified.

Razuprotafib (AKB-9778) Clinical Summary

- Razuprotafib administered by subcutaneous injection is highly bioavailable with a predictable, dose related pharmacokinetic profile.
- Razuprotafib has been dosed safely at single subcutaneous doses of up to 80 mg in healthy volunteers and 30 mg in patients with diabetes (BID for 28 days)
- Razuprotafib 15 mg QD or BID has been dosed safely for 12-48 weeks in over 250 patients with diabetic eye disease
- In diabetic patients dosed with 15 mg QD or BID, there has been clear evidence of target engagement and efficacy (lower blood pressure, reduced macular edema in combination with anti-VEGF therapy, and decrease in UACR and hsCRP)
- Razuprotafib drug substance has been scaled up to 10 kg batches, an amount sufficient for treating 10-12,000 patients for 14 days
- When prepared as a solution for injection in single dose, sterile syringes, Razuprotafib is stable at room temperature for at least 2 years, making storage and dosing convenient in the non-ICU or ICU setting
- In summary, razuprotafib is a Phase 2/3-ready drug that restores Tie2 activation to reduce inflammation and stabilize blood vessels providing breakthrough potential for reducing the severity of COVID-19 associated pulmonary and vascular pathology.

Why Razuprotafib?: Restoring Tie2 Activation Enhances Endothelial Function and Vascular Stability to Improve Outcomes in COVID-19

COVID-19: the vasculature unleashed

Laure-Anne Teuwen[1,2,3], Vincent Geldhof[1], Alessandra Pasut[1] and Peter Carmeliet[1,4]

On the basis of emerging evidence from patients with COVID-19, we postulate that endothelial cells are essential contributors to the initiation and propagation of severe COVID-19. Here, we discuss current insights into the link between endothelial cells, viral infection and inflammatory changes and propose novel therapeutic strategies.

Teuwen *et al. Nat Rev Immunol* (2020). https://doi.org/10.1038/s41577-020-0343-0

Tie2 Activation with Razuprotafib could Improve Outcomes in COVID-19 by Reducing:

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Vascular leakage
Endothelial cell dysfunction and loss
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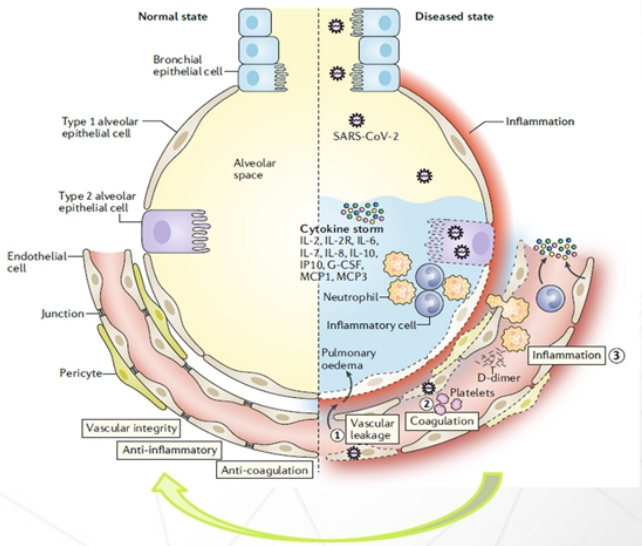
Pulmonary vascular resistance
V/Q mismatch
"Angiofibrosis"

all of which could improve the physiology and outcomes of patients with COVID-19.



Razuprotafib (AKB-9778)