



# PTC299 for COVID-19

Stuart W. Peltz, Ph.D., CEO

# Forward Looking Statement

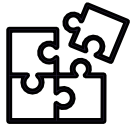
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# PTC299 for the Potential Treatment of COVID-19



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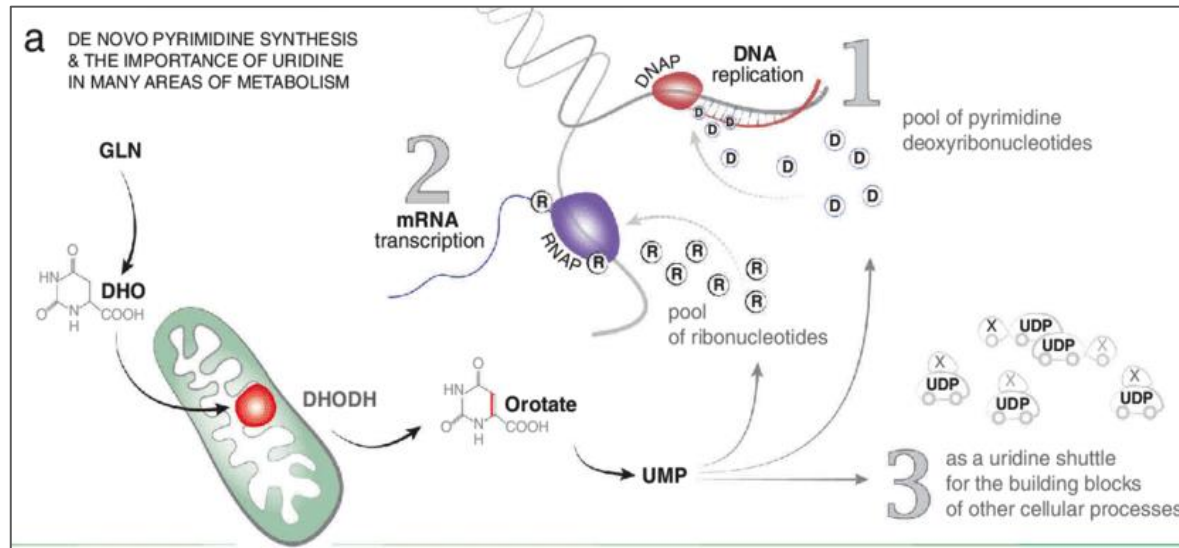


**Phase 2/3 clinical trial expected to initiate soon**

Multi-national Phase 2/3 clinical trial, which could support registration if positive, expected to initiate in the U.S. in the coming days

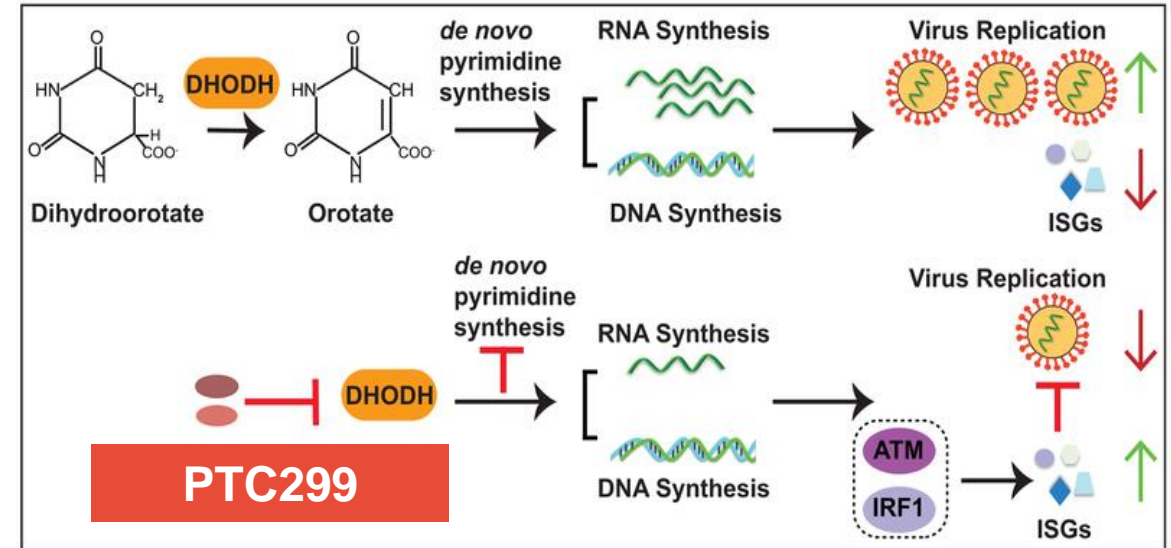
# PTC299 – Novel Dual Mechanism of Action

## Mechanism 1: Inhibition of viral replication through dihydroorotate dehydrogenase (DHODH)



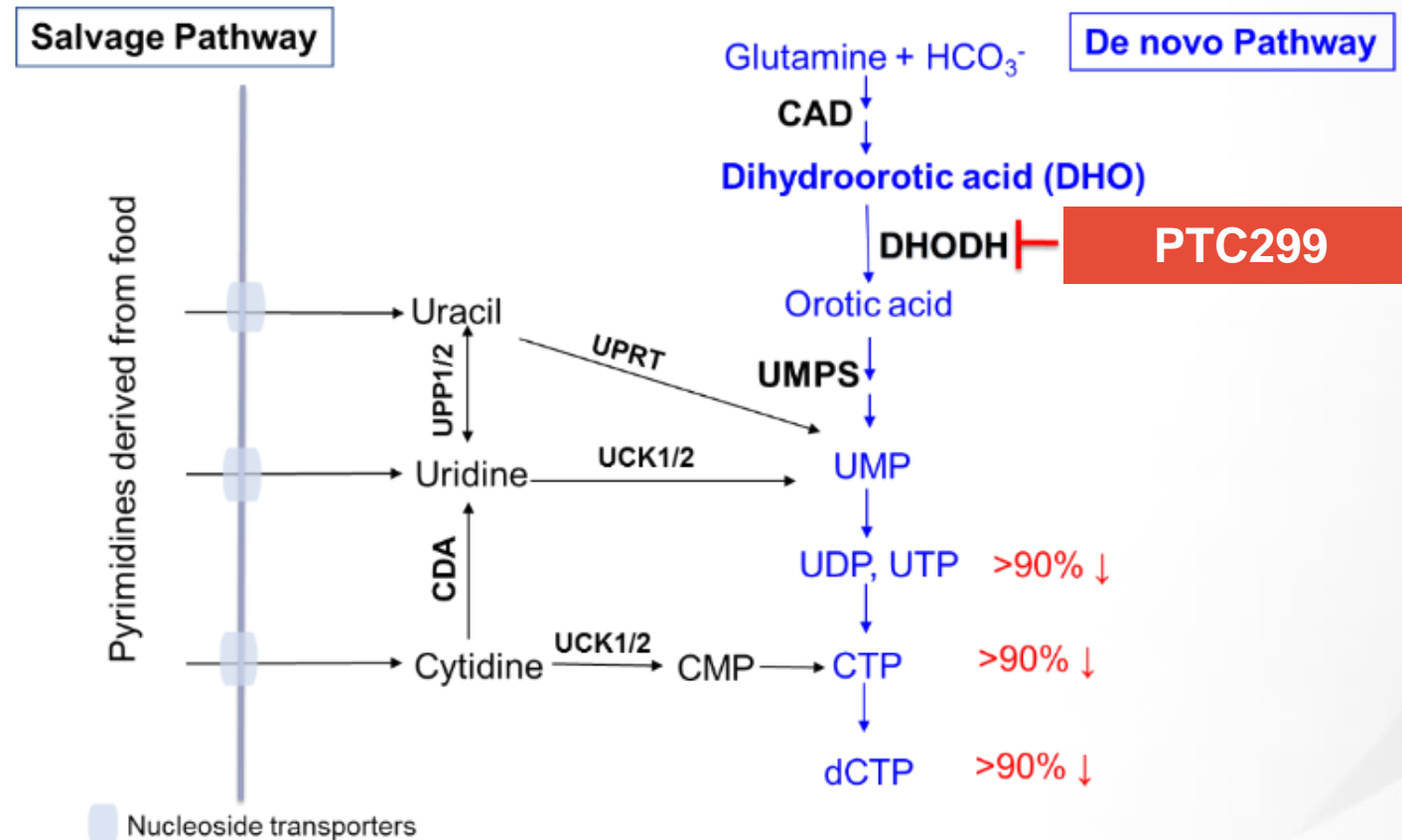
Source: Sykes, Expert Opin Ther Targets, 2018.

## Mechanism 2: Inhibition of the COVID-19 inflammatory response through DHODH



Source: Luthra et al, Antiviral Res, 2018.

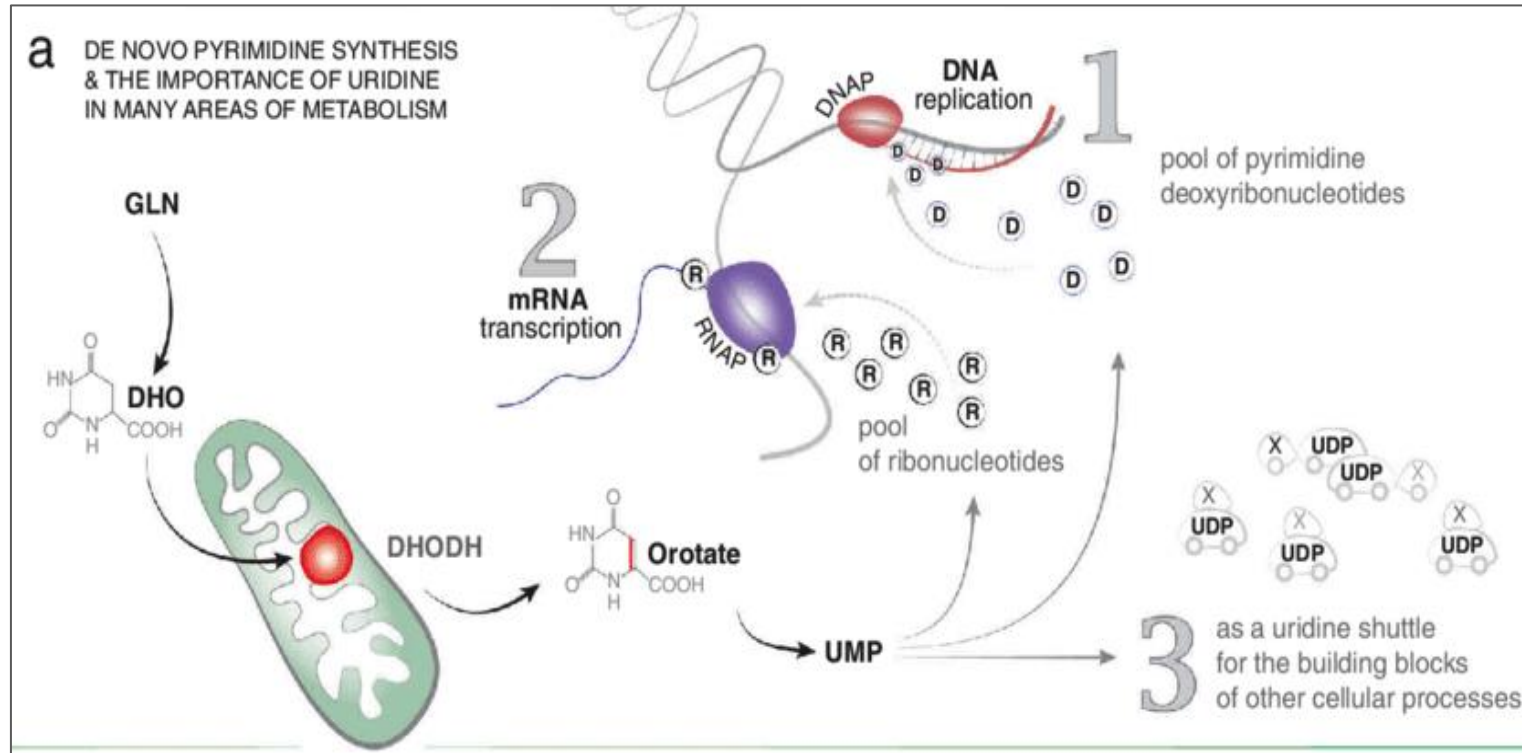
# DHODH is an Essential Cellular Enzyme in the De Novo Pyrimidine Nucleotide Synthesis Pathway



**Abbreviations:** CAD, complex of the following three enzymes: carbamoyl-phosphate synthetase 2, aspartate carbamoyltransferase, and dihydroorotase; CDA, cytidine deaminase; CMP, cytosine monophosphate; CTP, cytosine triphosphate; DHO, dihydroorotate; UDP, uridine diphosphate; UMP, uridine monophosphate; UPP, uridine phosphorylase; UTP, uridine triphosphate.



# Mechanism 1: Inhibition of Viral Replication Through DHODH



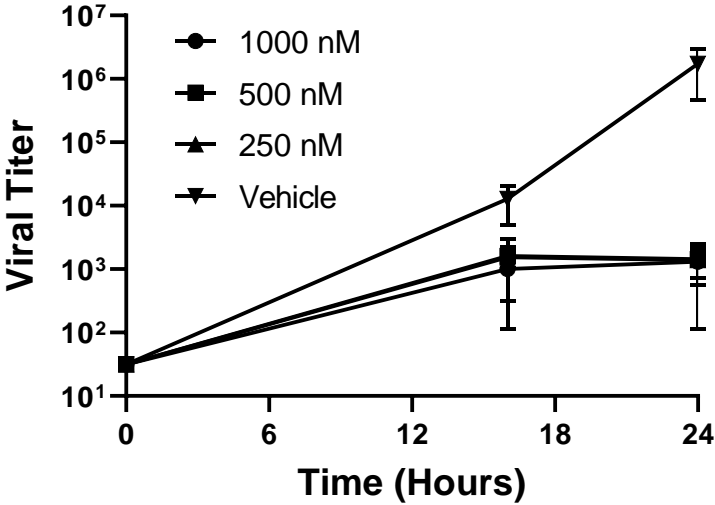
Source: Sykes, Expert Opin Ther Targets, 2018.

## DHODH inhibits viral replication

- Essential for RNA viral infections
- Central to the production of pyrimidines required for genome replication
- Inhibiting DHODH disrupts RNA synthesis and blocks viral replication

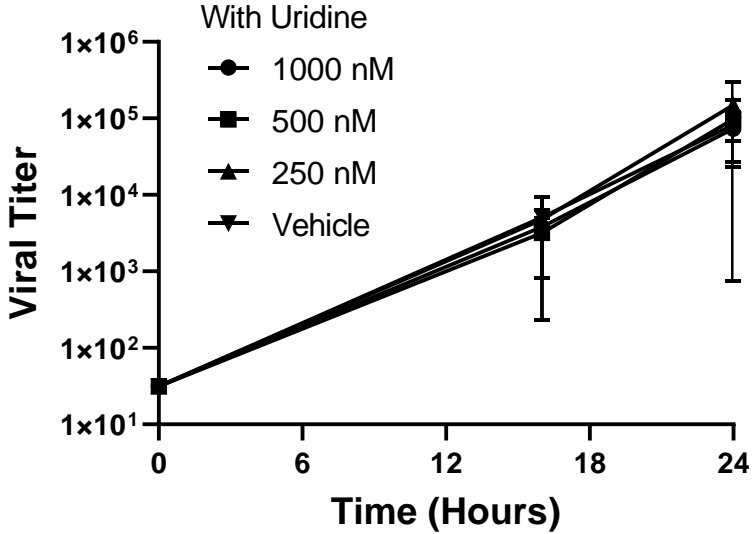
# PTC299 Reduces SARS-CoV-2 Virus Titer In Vitro

**Efficacy**

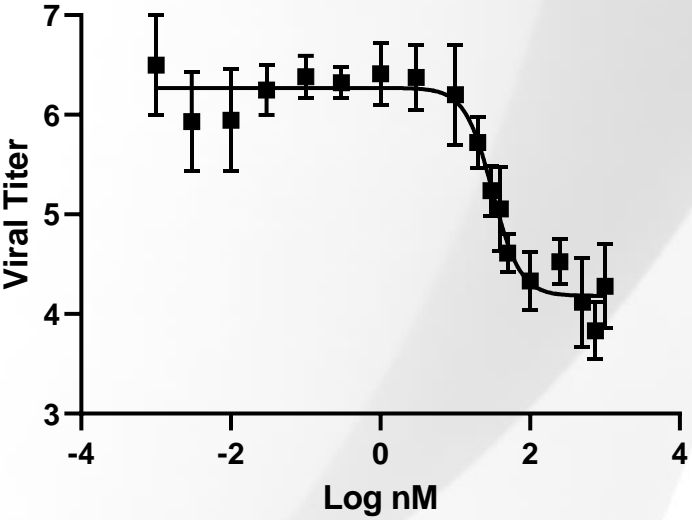


**3-log drop at 250 nM**

**DHODH Dependence**



**Potency**



**EC<sub>50</sub> was 2.6 nM**

# PTC299 Reduces Viral Infection Without Cytotoxicity

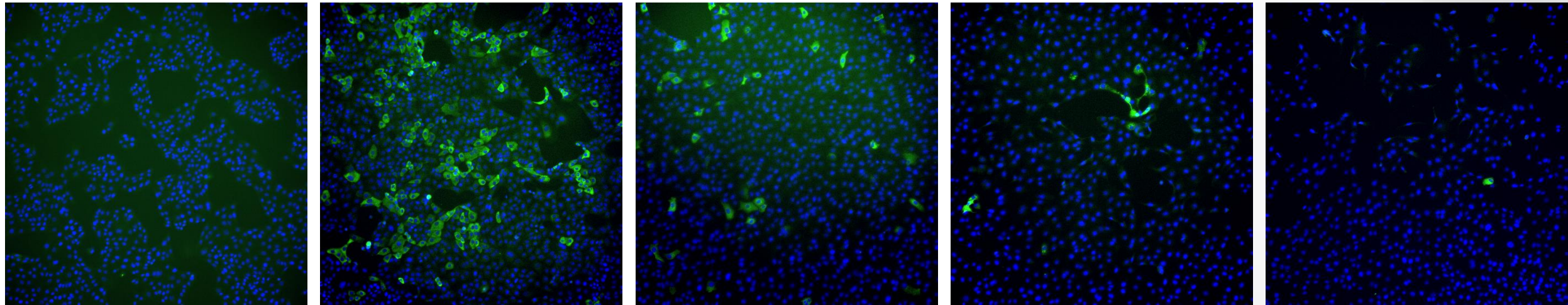
Uninfected

DMSO control

30 nM

300 nM

3  $\mu$ M

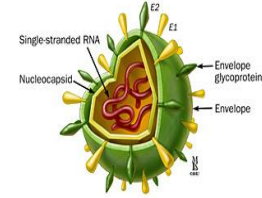




# PTC299 has Broad Spectrum Activity Against RNA Viruses\*



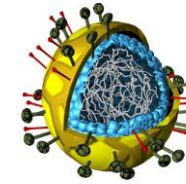
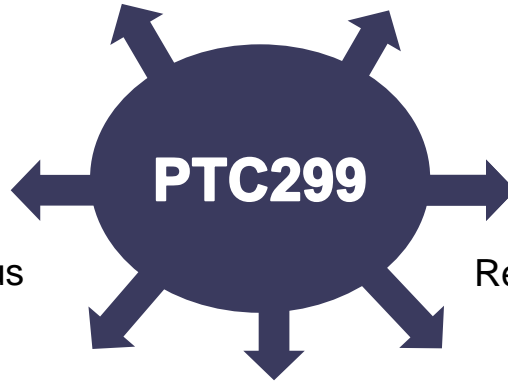
Parainfluenza virus 3  
 $EC_{50} = 34 \text{ nM}$



Hepatitis C virus  
 $EC_{50} = 36 \text{ nM}$



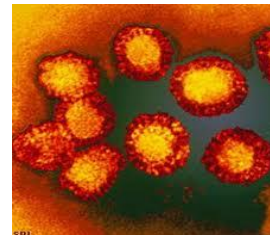
Rift Valley fever virus  
 $EC_{50} = 13 \text{ nM}$



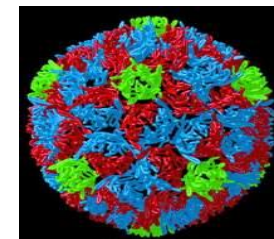
Respiratory syncytial virus  
 $EC_{50} = 430 \text{ nM}$



Ebola virus  
 $EC_{50} = 9.1 \text{ nM}$

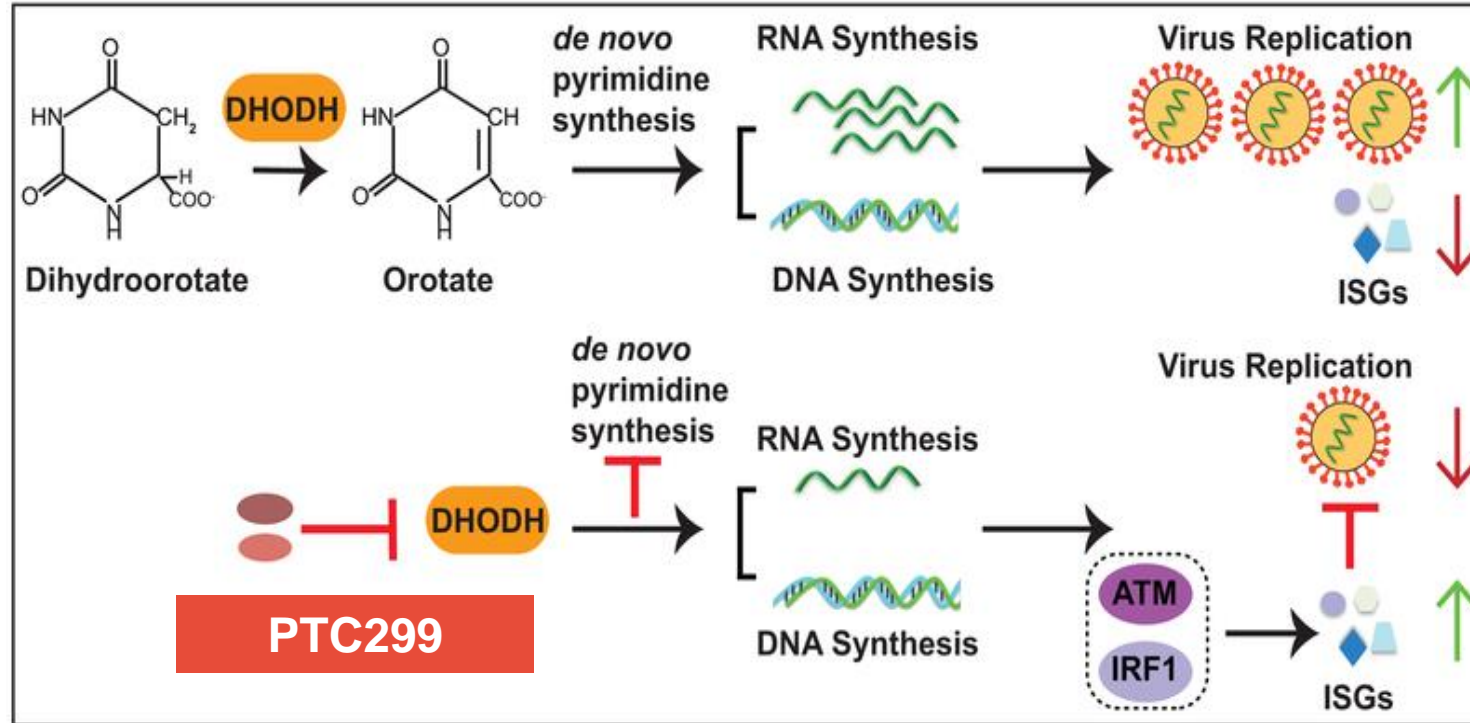


West Nile virus  
 $EC_{50} = 76 \text{ nM}$



Poliovirus  
 $EC_{50} = 0.57 \text{ nM}$

# Mechanism 2: Inhibition of the COVID-19 Inflammatory Response Through DHODH



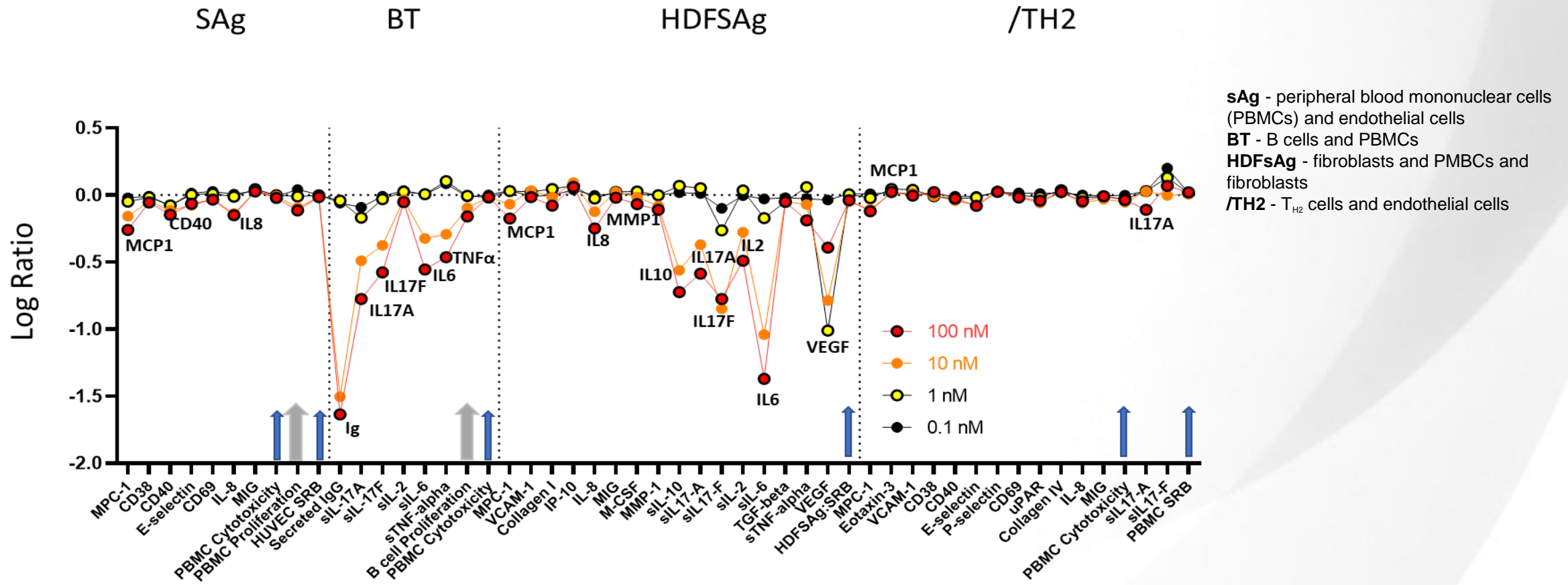
Source: Luthra et al, Antiviral Res, 2018.

## DHODH inhibits inflammatory cytokines

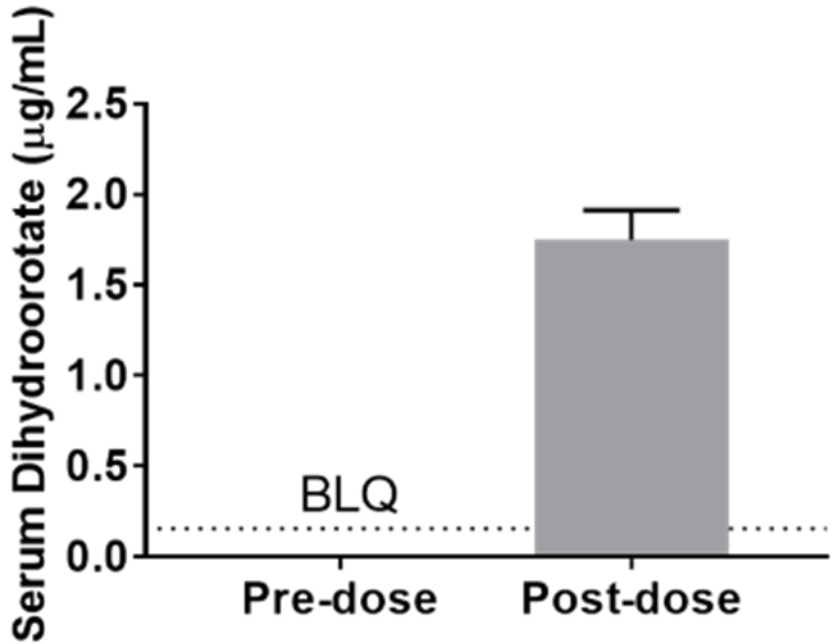
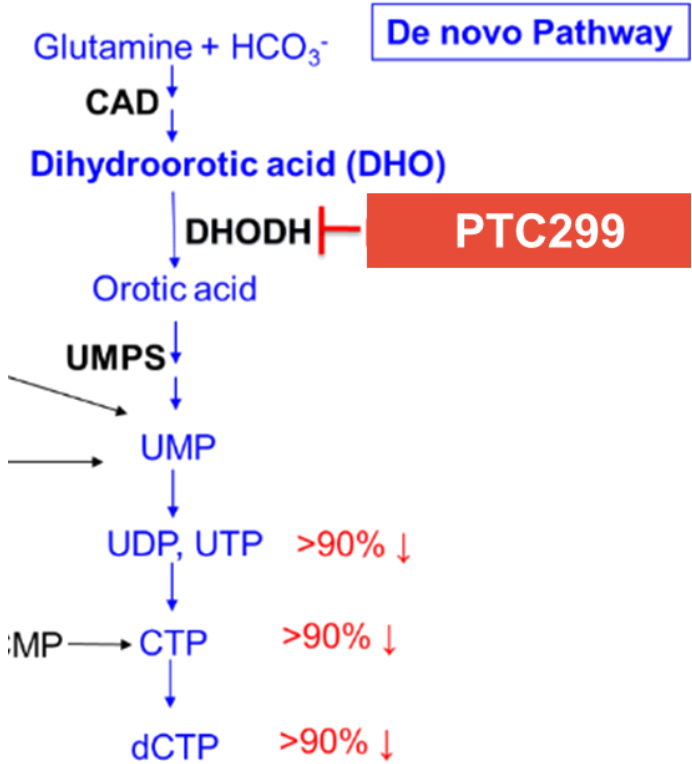
- Blocking pyrimidine depletion results in changes in inflammatory pathways
- Pyrimidine nucleotide *de novo* synthesis is necessary for virus proliferation

# PTC299 Inhibits Expression of Cytokines Critical in Over-reactive, Stress-induced Immune Response

Stress factors IL6, TNF $\alpha$ , IL17A, IL17F are inhibited by PTC299 in several primary human cell-based disease models



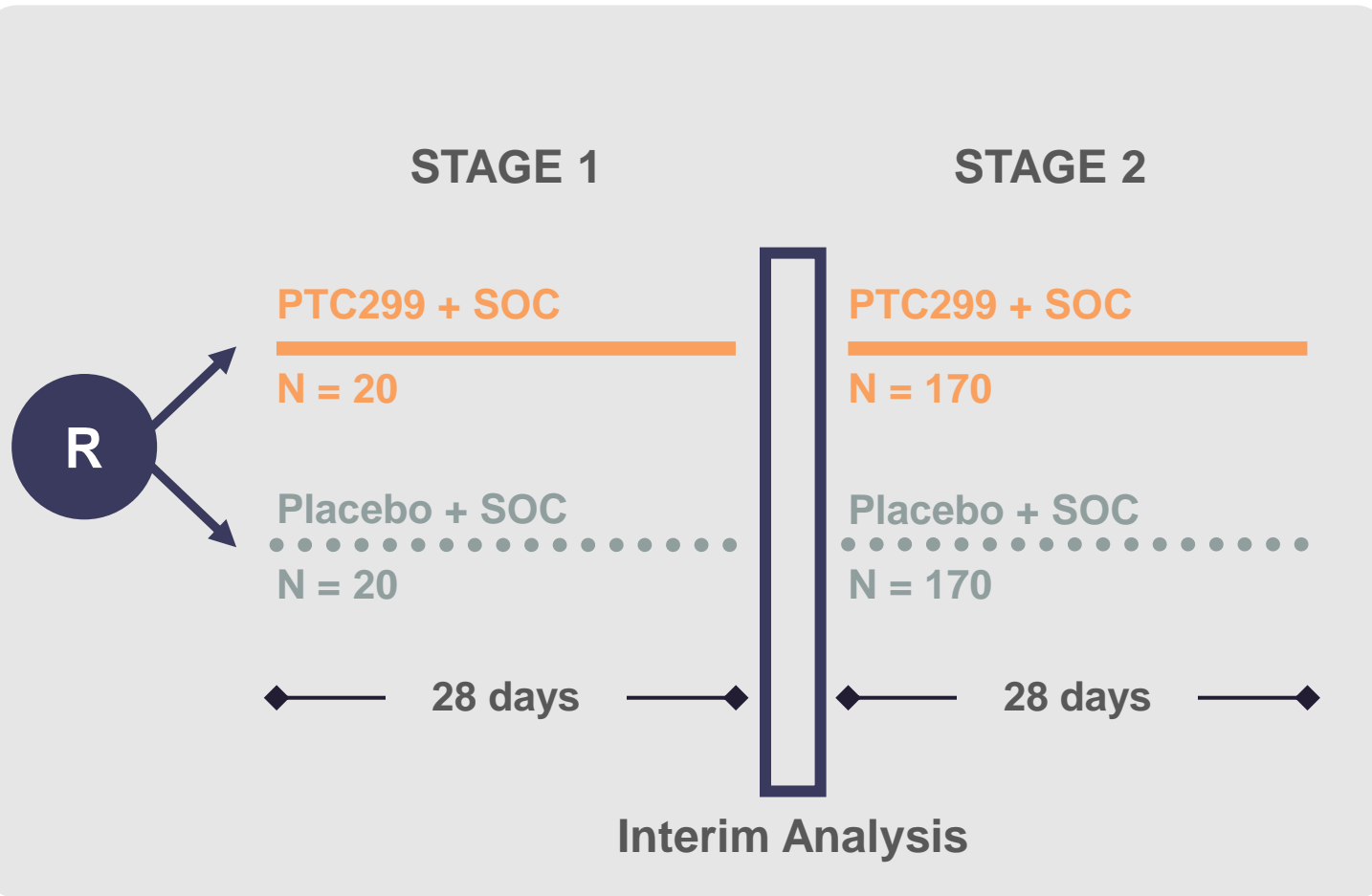
# PTC299 Exhibits Target Engagement in Patients and Appropriate Pharmacodynamic Effect



**Demonstrated increases in serum dihydroorotate (DHO)**

- Data in patients (n=5) treated with PTC299 demonstrated increases in DHO following treatment
- Indicates PTC299 in vivo target engagement and elicited appropriate pharmacodynamic changes in patients

# PTC299 COVID-19 Phase 2/3 Trial – FITE19

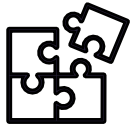


## Study Overview

- Randomized, placebo-controlled, multi-center, multi-national, two-stage study
- To evaluate efficacy & safety in hospitalized patients with COVID-19
- Primary endpoint: Time from randomization to respiratory improvement, defined as peripheral oxygen saturation  $\geq 94\%$  on room air, sustained until discharge from the hospital or the end of the study (Day 28)
- Interim analysis evaluating safety to follow first stage



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