

# Small Molecule Inhibitors of Prolyl Hydroxylase for Traumatic Brain Injury and Brain Ischemia

## Lead Inventors:

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## Background & Unmet Need

- There are many potential sources of injury to the brain associated with free radical production and subsequent oxidative damage
- Following intracerebral hemorrhage (ICH), red blood cells break down over time to release heme and highly reactive 'free' iron, which can cause oxidative damage to the brain
- In brain ischemia, hypoxia also favors the production of reactive oxygen species (ROS) which in turn increases oxidative stress, causing cell death
- Hypoxia inducible factor (HIF) Prolyl Hydroxylases (PHDs) canonically effect the degradation of HIF, but have recently been implicated as neuroprotective factors in other, HIF-independent pathways
- **Unmet Need:** Treatments to abrogate oxidative damage in hypoxia and hemorrhage-related brain injury

## Technology Overview

- **The Technology:** Novel inhibitors of HIF-PHDs for the treatment of TBI and brain ischemia
- **The Discovery:** The inventors have discovered a class of selective inhibitors of PHDs which protect against oxidative damage
- These branched oxyquinolines coordinate iron at the active site of HIF-PHDs, blocking their function
- These inhibitors suppress the ATF4 pro-death pathway and exhibit protective effects on mitochondrial function, indicating that they afford neuroprotection by an HIF-independent pathway
- **PoC Data:** In a mouse model of ICH, mice treated with PHD inhibitors had reduced numbers of degenerating neurons ( $p < 0.001$ ) and behavioral deficits ( $p < 0.05$ )
- In a model of oxytosis, a cell death pathway involving oxidative stress, PHD inhibitors restored mitochondrial ATP production and increased cell viability ( $p < 0.001$ )

## Inventors:

Rajiv R. Ratan  
Saravanan Karuppagounder

## Patents:

US Patent [10,716,783](#)

US Patent [9,505,741](#)

EP Patent [3,079,697](#)

EP Patent [2,891,649](#)

CN Patent [20118002045](#)

*Additional Patents in FR, DE, GB, CH*

## Publications:

[Karuppagounder et al. Sci Trans Med. 2016.](#)

[Neitemeier et al. Cell Death Dis. 2016.](#)

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## Cornell Reference:

D-4295, D-6127



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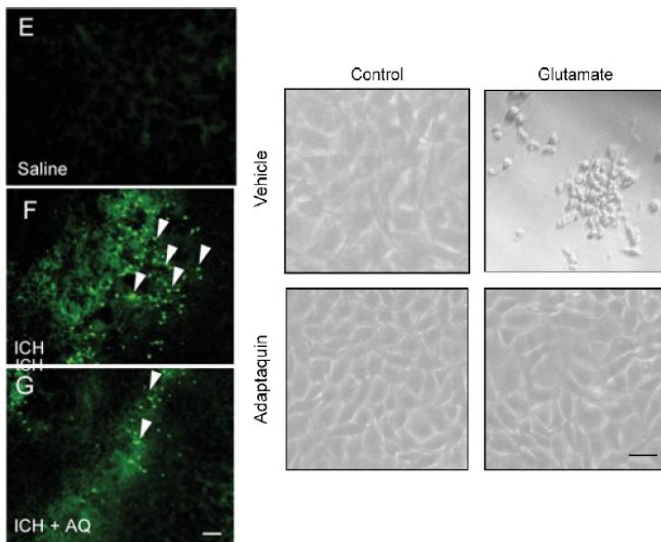
## Technology Applications

- Treatment of intracerebral hemorrhage or hemorrhage in other parts of the central nervous system
- Treatment of brain ischemia and cerebral hypoxia
- Treatment of neurodegenerative diseases associated with oxidative damage to mitochondria

## Technology Advantages

- PHD Inhibitors readily cross the blood-brain barrier
- PHD inhibitors are highly selective and have few off-target effects on iron distribution or global histone acetylation and methylation
- Inhibitors of the same target have demonstrated safety in clinical trials

## Supporting Data / Figures



**Figure 1:** Left: PHD inhibitors (AQ) protect against neuronal death. Degenerating neurons are marked by white arrows. Right: PHD inhibitors (Adaptaquin) protect against glutamate induced oxytosis.

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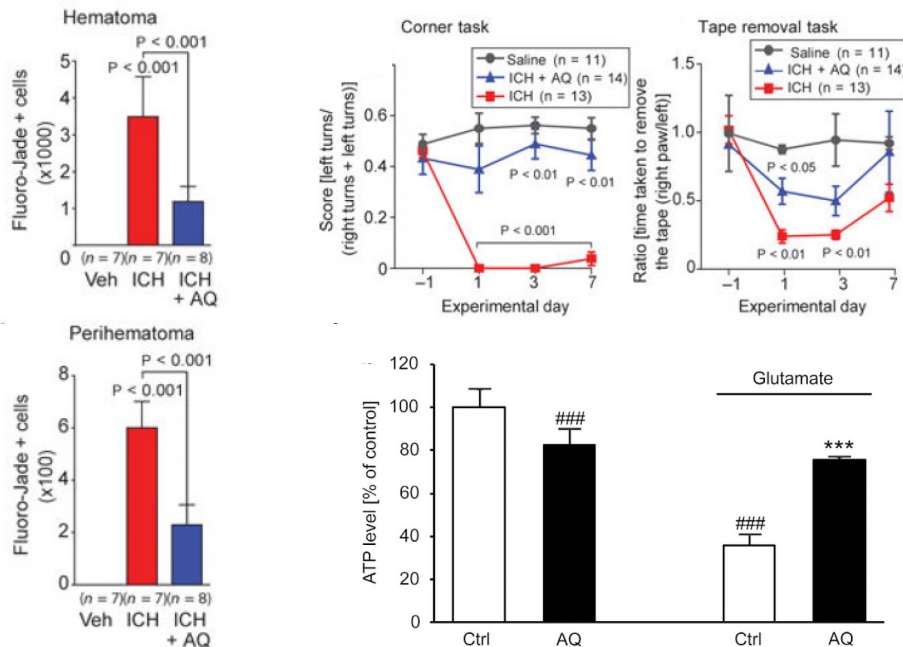
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## Supporting Data / Figures



**Figure 2: Left:** Mice treated with PHD Inhibitors (AQ) demonstrated reduced numbers of degenerating neurons **Top:** Mice treated with PHD inhibitors showed improved task performance following ICH **Bottom:** PHD Inhibitors (AQ) restore mitochondrial respiration, measured here by ATP production.

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# The Inhibitors of PHD program is supported by a robust international IP strategy and peer reviewed publications

## IP Status & Publications

- **Intellectual Property:**

- US Patent [10,716,783](#): “Prolylhydroxylase/ATF4 inhibitors and methods of their use for treating neural cell injury or death and conditions resulting.” (Anticipated Expiration: Dec 12, 2034)
  - Additional FR, DE, GB Patents [3,079,697](#): “Prolylhydroxylase/atf4 inhibitors for treating neural cell injury.”
- US Patent [9,505,741](#): “Prolylhydroxylase inhibitors and methods of use.” (Anticipated Expiration: Feb 17, 2031)
  - Additional CN Patent [20118002045](#) and FR, DE, CH, GB Patents [2,891,649](#): “Prolylhydroxylase inhibitors and methods of use
- Cornell Dockets: D-6127, D-4295

- **Publications:**

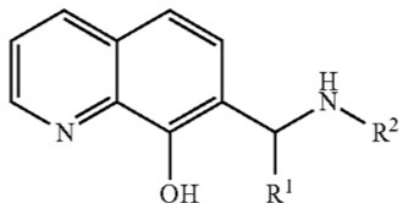
- [Karuppagounder et al.](#) “Therapeutic targeting of oxygen-sensing prolyl hydroxylases abrogates ATF4-dependent neuronal death and improves outcomes after brain hemorrhage in several rodent models.” *Sci Transl Med.* 2016.
- [Neitemeier et al.](#) “Inhibition of HIF-prolyl-4-hydroxylases prevents mitochondrial impairment and cell death in a model of neuronal oxytosis.” *Cell Death Dis.* 2016.



# Issued international patents include granted composition of matter and method claims

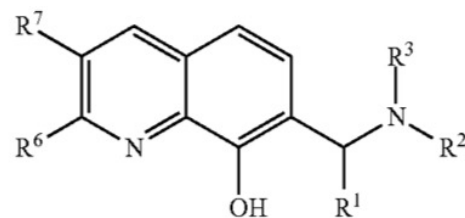
## US 10,716,783

1. A method for treating a patient suffering from mild traumatic brain injury, the method comprising administering to said patient an effective amount of a HIF prolyl-4-hydroxylase inhibiting compound having the following general formula:



## US 9,505,741

1. A method for treating a patient having brain ischemia, the method comprising administering to said patient in need thereof an effective amount of a HIF prolyl-4-hydroxylase inhibiting compound within the following general formula:





**Weill  
Cornell  
Medicine**