

Astrocyte Pharmaceuticals, Inc.

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Harnessing the stars to treat traumatic brain injuries

New company Astrocyte Pharmaceuticals is pioneering a novel approach to healing a damaged brain that involves activating energy supplies in astrocytes, the abundant star-shaped brain cells with a central role in repairing CNS injury.

Football impacts and car crashes are just some events that can cause traumatic brain injuries (TBIs). Many news stories from the past few years about TBIs and concussions (a mild form of TBI) have emerged as researchers have learned more about the disturbing long-term effects of repetitive injuries, which can trigger age-associated neurodegeneration resulting in a range of symptoms and disabilities over decades¹.

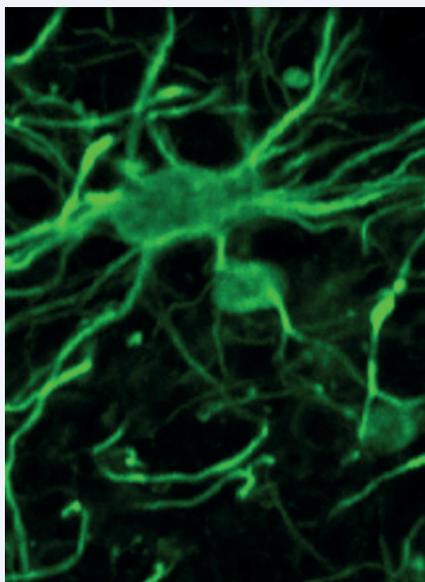
Each year, approximately 1.7 million people are diagnosed with a TBI in the United States, according to the US National Institutes of Health². The incidence of this type of injury is even more widespread when those who are not treated in a hospital or emergency department are included, with up to 3.8 million concussions occurring each year in the United States³. Despite the growing need, there are no approved therapeutics for the treatment of TBI.

That's where Astrocyte Pharmaceuticals, Inc. may be on to something exciting and very promising. Historically, neuroprotective approaches have focused on nerve cells or just one mechanism involved in a brain injury. "Our approach is different," said Jeffrey L. Ives, an independent director at Astrocyte. "Instead of trying to help neurons directly by regulating the release of neurotransmitters or the influx of calcium, our work focuses on activating astrocytes, which are the super custodians of the brain."

Spawnd by the research of cofounder James D. Lechleiter, which was patented in 2013, Astrocyte's novel approach targets P2Y₁ receptors on astrocyte cells, which are abundant in the brain. These specialized star-like glial cells can outnumber nerve cells five to one in many areas throughout the brain⁴ and are essential for vital aspects of maintaining brain health and function, from adjusting blood flow to regulating neurotransmitter transport and uptake to providing energy. Astrocyte's compounds trigger multiple intrinsic protective pathways in the brain, increasing the chances for success. "This is an exciting pleiotropic mechanism, and our goal is to harness the neuroprotective and neuroregenerative support of astrocytes through our proprietary target and small-molecule agonists," said William S. Korinek, Astrocyte's cofounder and CEO.

Brain injury after impact

When the brain endures an impact, often there is tearing of blood vessels and bruising, as well as a flood of potassium, which overexcites nerve cells and triggers the release of toxic levels of glutamate. Studies have shown that without



Astrocytes, easily recognized by their stellate structure with many protrusions branching radially out from the soma, form a supportive network throughout the brain.

astrocyte intervention, nerve cells are permanently damaged under such circumstances⁵. Astrocytes have a vital role in removing excess glutamate and other neurotransmitters, regulating calcium release, restoring ion balance and controlling brain edema or swelling. Astrocytes require energy to perform these functions, and Lechleiter found that boosting ATP production by using a P2Y₁ receptor agonist to selectively activate mitochondria metabolism in astrocytes is remarkably effective at protecting the brain.

"Normally people want to block pathways to stop injury," Lechleiter said. "We're saying, let's stimulate the natural caretakers of the brain, part of whose job is to help maintain ion homeostasis, which fundamentally controls edema." When the brain swells, it expands against the skull and puts additional pressure on neurons and tissues. Edema can result from even mild blows to the head, and if left untreated, the swelling can cause many symptoms from headaches to behavioral changes.

"The sooner you provide treatment, the better, but we still see improvements when treating 24 hours after the initial trauma," said Lechleiter. P2Y₁ receptor activation increases neuronal and astrocyte survival, and it also partially reverses neuronal and glial damage. Ives emphasized that the pharmacology of Astrocyte's lead candidate is

compelling, and he mentioned that the Lechleiter lab at the University of Texas Health Science Center at San Antonio has rescued or repaired neurons that in the past would have been considered damaged beyond help, even two days after trauma.

Future development

Astrocyte has conducted a number of initial studies in mouse models and ex vivo human brain tissue and is planning further rodent and porcine studies. "The neuroprotection data to date in multiple models is quite compelling and promising," expressed Ives. These initial steps have provided a robust data foundation and strong rationale to expect translation to people, and to support the move toward clinical trials, which the company is aiming to start in 2017.

The potential for an efficacious neuroprotective therapeutic would also extend beyond TBIs, as neuronal damage or loss is central to many CNS disorders. "It's exciting that a new therapeutic might not only help the millions of brain trauma patients but also those with other disorders, such as stroke and neurodegenerative diseases," said Korinek. "This urgent medical need is the driving force behind our commitment and approach."

Many other groups, from sports leagues to the US government, have also shown their support for more of this type of critical research. Astrocyte Pharmaceuticals stands out with a fresh and compelling hypothesis of neuroprotection that has the potential to reach the ultimate goal of healing a damaged brain.

References

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