BIOCENTURY

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BIOINTERVENE TAKES ON ADENOSINE IN PAIN, RAISES $30M

With IP from St. Louis University and NIH, BioIntervene raised a $30 million series A round from MPM Capital to bring what could be a first-in-class pain therapy into the clinic.

The company plans to start a Phase I neuropathic pain trial next half of lead candidate BIO-205, an adenosine A3 receptor (ADORA3) agonist. The offering is expected to give BioIntervene enough runway to complete proof-of-concept studies.

MPM's Ed Hurwitz, who serves as executive chairman of BioIntervene Inc., told BioCentury the firm was attracted by the novel biology the company had elucidated for the adenosine receptor, and because it had a development candidate in-hand.

There are several small molecule ADORA3 agonists in clinical development, though most are for autoimmune diseases or liver indications. ADORA3 has also recently been explored for inflammation; it is one of several novel targets in early-stage testing for osteoarthritis.

Can-Fite BioPharma Ltd. is developing preclinical allosteric ADORA3 modulator CF602, which has both anti-inflammatory and cartilage-protecting properties. Several studies have shown that the adenosine pathway is involved in cartilage homeostasis, and high levels of the nucleoside may cause cartilage destruction (see **"New Targets in Osteoarthritis"**).

"This is the first group that has had the tools and foresight to explore the pharmacology of ADORA3 for treating pain."

Ed Hurwitz, MPM Capital

BioIntervene was founded in 2014 to house the fruits of a collaboration between St. Louis and NIH, which resulted in the development of compounds 10,000-fold more selective for the A3 receptor over other subtypes. Thanks to the selective compounds, founder Daniela Salvemini was able to show that the A3 receptor was driving the analgesic properties, Hurwitz said. Salvemini is a professor of pharmacology and physiology at St. Louis.

"This is the first group that has had the tools and foresight to explore the pharmacology of ADORA3 for treating pain and other inflammatory conditions," Hurwitz said.

DISSECTING THE ADENOSINE PATHWAY

Salvemini's research has shown that in response to injury, adenosine kinase is upregulated in the CNS, particularly within astrocytes. Phosphorylation of adenosine in astrocytes leads to a lower adenosine concentration in the synapse and reduced signaling via neuronal adenosine receptors (see Figure: "How agonizing ADORA3 normalizes the adenosine pathway").

The findings add to a growing list of roles astrocytes play in disease biology. Interest in the cell type, along with microglia, another immune-like cell that drives neuroinflammation in the CNS, has been growing among academics and drug developers (see **"The Next Wave in Neurodegeneration Expands Beyond Neurons"**; **"AstronauTx Launches to Target Astrocytes"**).

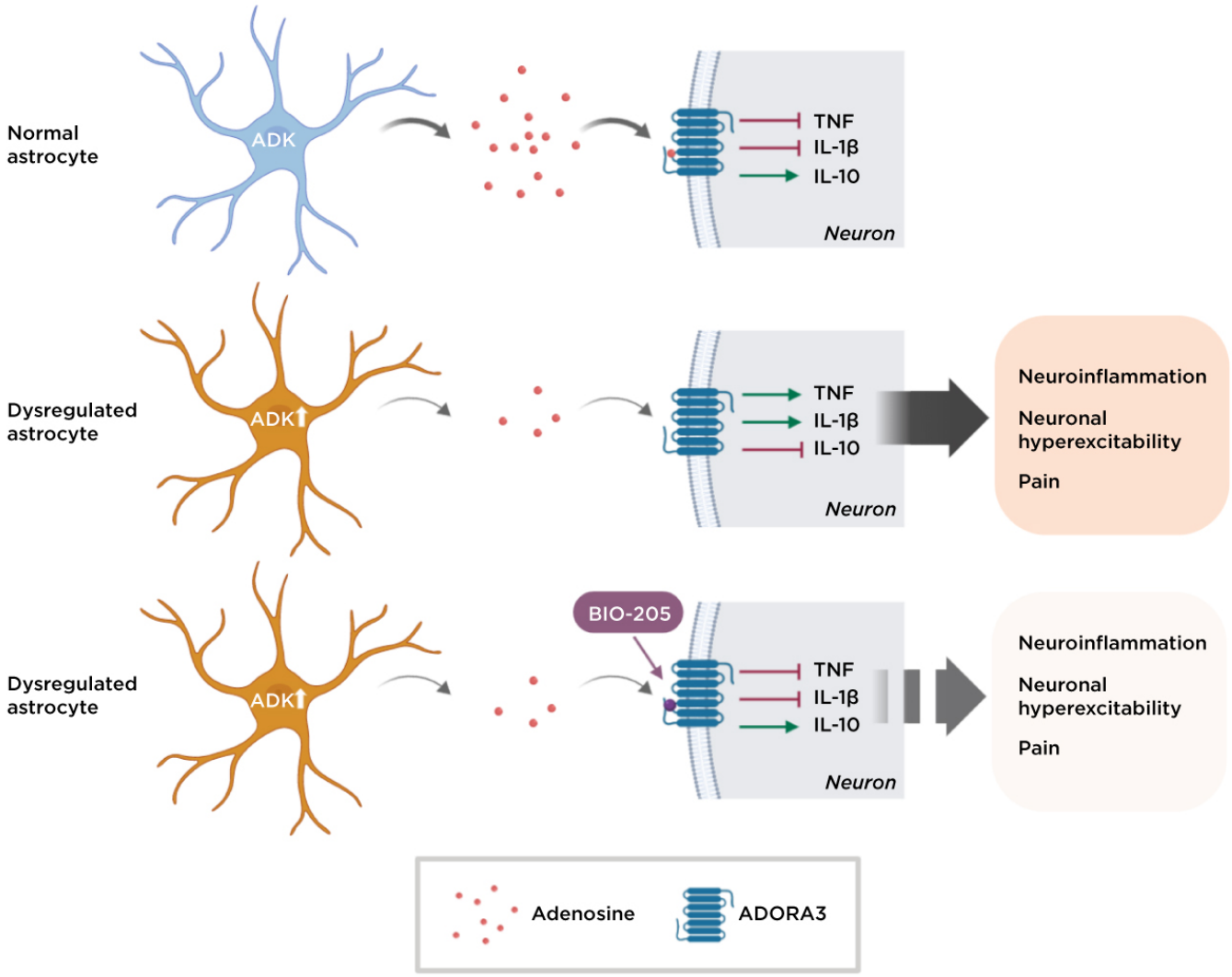
Figure: How agonizing ADORA3 normalizes the adenosine pathway

Work by BioIntervene Inc. scientific founder Daniela Salvemini, a professor of pharmacology and physiology at St. Louis University, has identified a pathway that leads to neuropathic pain via disruption of adenosine A3 receptor signaling in neurons.

In response to injury, chemotherapy or other triggers of neuropathic pain, astrocytes become dysfunctional and upregulate adenosine kinase. The phosphorylation of adenosine in astrocytes leads to lower concentrations of the molecule in the synapse and reduced signaling via ADORA3.

As ADORA3 regulates several cytokines, this leads to a pathologic, proinflammatory environment.

BioIntervene aims to restore normal ADORA3 signaling via lead compound BIO-205, a selective ADORA3 agonist.



While it was already known that adenosine was involved in pain, researchers had thought the mechanism was tied to the A1 receptor. But agonists of ADORA1 had all failed in the clinic, partly because the receptor is expressed on heart tissue and its activation leads to cardiovascular side effects.

Salvemini said that prior to her work, the A3 receptor's role in pain had been relatively unexplored for several reasons, including lack of adequate tools.

"That's what piqued my interest," she said. "I wanted to know if other receptor subtypes could play a role."

She began investigating the pathway in 2010 and found that a tool ADORA3 agonist had promising activity in preclinical models. Shortly after, she partnered with Ken Jacobsen at NIH to develop more potent agonists.

Salvemini has since published several papers, including a 2018 **article** in *PAIN*, that map out how agonizing ADORA3 inhibits the release of neuroexcitatory cytokines, including TNF and IL-1β, and increases levels of IL-10, a neuroprotective cytokine.

"What we're doing is shifting the balance of a pro-inflammatory medium to a powerful, endogenous anti-inflammatory medium in the brain," Salvemini said.

Compared to other subtypes, ADORA3 is expressed at low levels in normal tissues. The receptor is also upregulated in response to injury, which makes it ideal for a targeted therapeutic, Salvemini said.

She thinks ADORA3 agonism could also be applicable to inflammatory diseases like arthritis and psoriasis, as well as cancer.

BioIntervene is starting with neuropathic pain because it has been a focus of Salvemini's research, and because patients have few treatment options.

MPM has invested in the pain space before, Hurwitz said, and the firm was struck by BioIntervene's animal data. In a model of neuropathic pain, BIO-205 was more efficacious and potent than gabapentin or morphine; and when combined, the compound had a synergistic effect with both painkillers.

Hurwitz added that another draw was that BIO-205 is not an opioid.

The funds will also go toward advancing the biotech's portfolio of ADORA3 agonists in several chronic inflammatory and neurodegenerative indications.

BioIntervene also announced the hire of Charles Cohen as CSO Monday. He was VP of biology at neurology company Xenon Pharmaceuticals Inc. (NASDAQ:XENE) and has also worked at Vertex Pharmaceuticals Inc. (NASDAQ:VRTX), Merck & Co. Inc. (NYSE:MRK) and Bayer AG (Xetra:BAYN).

MPM's Gary Patou serves as CMO.

TARGETS

ADORA3 - Adenosine A3 receptor

ADORA1 - Adenosine A1 receptor

IL-1β - Interleukin-1 beta

IL-10 - Interleukin-10

TNF - Tumor necrosis factor