CELL & GENE THERAPY INSIGHTS

Exploring asprosin: how AAV vectors are advancing hormone research

INTERVIEW

"I do believe AAV vectors will become more widely used, not just for CGTs but in other applications as well."

Lauren Coyle, Editor, BioInsights, speaks to **Bijoya Basu**, MD-PhD Candidate, Case Western Reserve University School of Medicine, about the potential of AAV vector technology in hormone research and translational science, particularly when studying asprosin, a hormone with roles in metabolism, appetite, and thirst regulation.

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Q Why has asprosin captured the attention of researchers across multiple disease areas?

BB The asprosin hormone was discovered around a decade ago by Dr Atul Chopra, the principal investigator in our laboratory. It was found serendipitously—there was a patient with a unique disease called neonatal progeroid syndrome (NPS), and at the time, nobody knew what was causing it. Then, simply by studying the genetics of this rare condition, we discovered the asprosin hormone exists in all bodies.

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Asprosin is part of a class of hormones called caudamins [1], which are C-terminal cleavage products of unrelated proteins. Profibrillin is cleaved into two distinct products: fibrillin-1 from the N-terminus, which contributes to the extracellular matrix, and asprosin from the C-terminus [2].

What made asprosin interesting in the beginning was that it gave insights into human biology and metabolism. However, since it is a hormone, it also raised new questions of how it can be targeted and sequestered for therapeutic purposes. One of the early questions following its discovery was whether downregulating asprosin could lead to a potential therapy for type 2 diabetes and obesity [3].

As asprosin biology continues to unravel, more information is being revealed that this hormone is involved in significantly more than just metabolism. For example, a recent study found that it controls thirst in the brain through the cerebellum [1]. These studies are helping us not only to understand asprosin but also human biology, as a whole.

Q One major challenge in cell and gene therapies (CGT) is the variability of recombinant protein production. How has this impacted efforts to study asprosin, and how has this led your team to explore AAV as a solution?

BB One issue often seen with recombinant proteins is significant batch-to-batch variability. We have experienced this firsthand—after purchasing recombinant asprosin from different vendors, we found that its efficacy was inconsistent, and it only worked as expected in some cases. Rather than investing time troubleshooting or attempting to produce our own recombinant protein, we began considering alternative tools to study asprosin.

When studying asprosin, our goal was to modulate its pathway by either upregulating or downregulating. To this end, we employed various tools and strategies, including the use of genetic models and monoclonal antibodies [4,5] Ultimately, we adopted AAV vectors as a robust research tool to stably express asprosin in animal models and study its downstream effects manufactured and produced by Vector Biolabs. Unlike adenovirus, AAV does not induce illness in mice and provides long-term expression. Based on our observations, injecting mice with AAV allows for asprosin to be upregulated for several months. This has been instrumental in not only advancing our understanding of asprosin biology, but also in optimizing a variety of tools.

In our paper on the discovery of specific monoclonal antibodies [3], we utilized AAV to elevate circulating asprosin levels and subsequently neutralized them using the antibody. More recently, we have focused on optimizing the ELISA method we use to measure circulating asprosin [6]. The AAV was used as a tool to both elevate levels of asprosin and to demonstrate that our ELISA technique can reliably detect those changes.

Q How does AAV-mediated overexpression of asprosin overcome the reproducibility issues seen with recombinant approaches, and are there any specific benefits to using AAVs in hormone research more broadly?

BB As with any biological tool, there is always the possibility of batch-to-batch variability. However, in our experience using AAV over the past few years, we have found that almost every batch produced by Vector Biolabs has worked consistently. Our AAV-based tool enables stable overexpression *in vivo*, allowing for more consistent mechanistic studies. This results in consistently stable and elevated levels of the hormone.

In contrast, recombinant proteins typically involve administering a single dose. However, these are rapidly cleared from circulation, requiring administration of multiple doses to maintain physiological effects. AAV addresses reproducibility challenges by enabling chronic overexpression.

While AAVs are commonly associated with gene manipulation, typically for diseases involving defective or absent gene expression, our use of AAV in asprosin research is different. We are not editing a faulty gene but rather increasing the levels of a naturally occurring hormone in mice. It allows us to use AAV as a powerful way to learn more about biology itself.

According to our analyses, AAV administration results in approximately a two-fold increase in circulating asprosin. Interestingly, this mirrors the elevation observed in patients with obesity, who typically show around double the asprosin levels compared to individuals with normal weight. By replicating this condition in mice, we are able to study the hormones effects in a controlled and targeted manner. The mice do gain weight following AAV-mediated asprosin overexpression, but not to the extent seen in diet-induced obesity models [3]. This distinction allows us to isolate the effects of asprosin from other factors associated with obesity, such as systemic inflammation or metabolic dysregulation.

All things considered, AAV is a valuable tool in hormone research. It enables the hormone of interest to be elevated without significantly disturbing other physiological systems, thereby enhancing both experimental reproducibility and biological insight.

Q What has the use of AAV vectors revealed about asprosin's role in regulation that previous methods could not capture clearly?

BB With the AAV, we have seen increases in both blood glucose and body weight [3]. This has been shown across multiple studies from our laboratory over several years. We used multiple tools to prove this, including knockout models, monoclonal antibodies, and the AAV. Across our work, we have also demonstrated that when asprosin is downregulated in a mouse model, and we reintroduce it using AAV, certain physiological responses could be replicated upon reintroduction.

By chronically increasing asprosin levels with AAV, we have repeatedly observed rises in water intake, body weight and blood glucose. Importantly, we have also shown that these effects can be reversed—when we neutralize asprosin using tools like the monoclonal antibody, those phenotypes come back down [3]. In contrast, we would not necessarily be able to demonstrate this as clearly with recombinant protein, as we cannot be sure how long it remains elevated or how consistently it is being sequestered.

"I see firsthand how rapidly the field of CGT is evolving."

Furthermore, we have found that asprosin also increases appetite, and it does so through AgRP neurons [5]. Similarly, we have observed that mice injected with the AAV not only have higher body weight and blood glucose, but they also exhibit increased food intake, indicating a higher appetite [3].

Q Given your success with AAVs in asprosin research, do you see this platform being applicable to other emerging hormones or bioactive molecules, and what makes it suited for understudied targets?

BB I do believe AAV vectors will become more widely used, not just for CGTs but in other applications as well. Using it as an overexpression tool is very beneficial, especially when trying to uncover new biological insights. When asprosin was first discovered, there was some pushback—certain people did not believe that a hormone could come from the C-terminus of another protein.

It was necessary to have all these layers of proof because we were challenging what was already known in biology. AAV is a valuable tool for that, as it allows you to overcome some of the issues we discussed with recombinant proteins. It also enables chronic expression, which can be targeted later. Additionally, it helps optimize other tools, such as antibodies and ELISA. Therefore, I truly believe AAV will be an invaluable tool for researchers in the future.

Lastly, as mentioned earlier, asprosin forms during the specific cleavage process of profibrillin, which could explain why recombinant proteins sometimes present issues. As we continue to discover not only new hormones but also new ways hormones are secreted, having tools to overexpress them could be crucial for the field, instead of just relying on recombinant proteins.

Q Looking ahead, how do you see the role of AAV-based tools evolving in translational science, especially as CGTs continue to gain traction in both research and clinical settings?

BB One of the main advantages of AAV over vectors such as an Ad5 virus is its favorable safety and durability profile. While Ad5 can express transgenes more rapidly, it often induces immune responses and can make animals ill. In contrast, AAV tends to be well-tolerated and supports long-term expression, making it particularly valuable for both research and therapeutic applications.

As someone currently doing a PhD in genetics, I see firsthand how rapidly the field of CGT is evolving. New therapies are being approved at an accelerated pace, and the momentum in this space is significant. I believe AAV-based approaches will continue to contribute to both research and clinical understanding. This is particularly relevant as AAV becomes increasingly common in neuroscience and endocrinology research.

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BIOGRAPHY

Bijoya (Bijou) Basu is an MD-PhD candidate at Case Western Reserve University, currently pursuing a PhD in Genetics and Genomic Sciences. Her research, mentored by Dr Atul Chopra at the Harrington Discovery Institute, focuses on the hormone asprosin. Bijou's work has earned recognition through national presentations and publications, including in *Nature Neuroscience* and *Trends in Endocrinology and Metabolism*. She's received multiple accolades, including awards from the American Academy of Neurology and Society for Neuroscience. Bijou is committed to a career at the intersection of neuroscience, translational research, and patient advocacy.

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AUTHORSHIP & CONFLICT OF INTEREST

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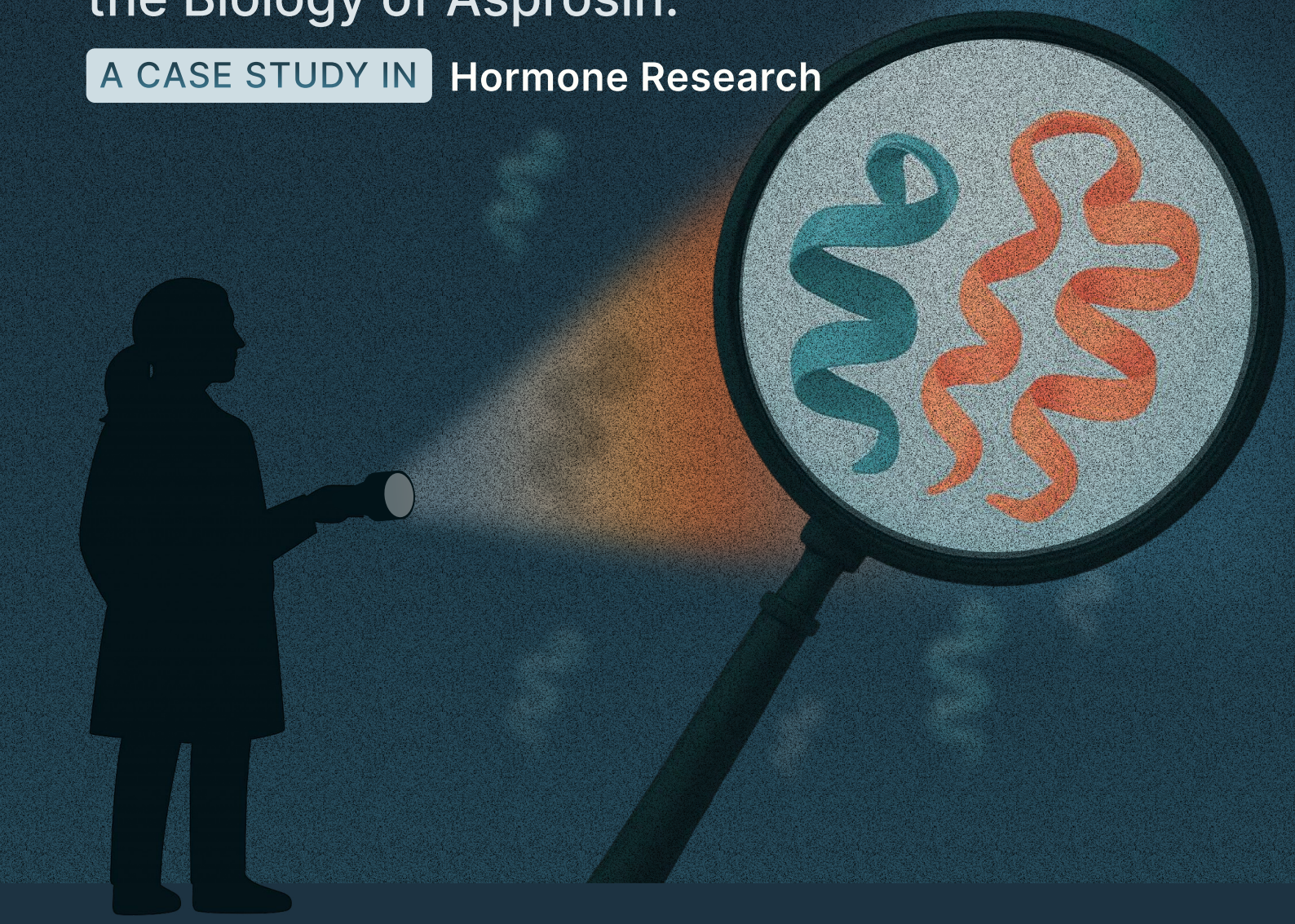
From Mystery to Discovery

AAV Makes It Clear

Harnessing AAV to Uncover the Biology of Asprosin:

A CASE STUDY IN **Hormone Research**



Bijoya (Bijou) Basu

Key Speaker