Vasopressin 1a Receptor (V1aR) Antagonists Reduce Neuronal Damage and Prevent Functional Deficits After Mild TBI

Neal G. Simon, Ph.D.
Chief Executive Officer
Azevan Pharmaceuticals, Inc.

Military Health Systems Research Symposium
August 6, 2026

DISCLOSURES

FUNDING: The U.S. ARMRAA is the awarding and administering acquisition office. This work is supported by The Assistant Secretary of Defense for Health Affairs endorsed by the Dept. of War through the Peer Reviewed Medical Research Program under Award Number HT9425-24-1-0617. Opinions, interpretations, conclusions, and recommendations are those of the author(s) and are not necessarily endorsed by The Asst. Secretary of Defense for Health Affairs or endorsed by the Dept. of War. In conducting research using animals, the investigator(s) adhere(s) to the laws of the US and regulations of the Department of Agriculture.

FINANCIAL: N.G. Simon holds equity, serves as an Officer and Board member, and receives compensation from Azevan Pharmaceuticals, Inc.

OTHER: Compound designations are anonymized for intellectual property purposes.

TRAUMATIC BRAIN INJURY

A Major Military and Civilian Healthcare Problem

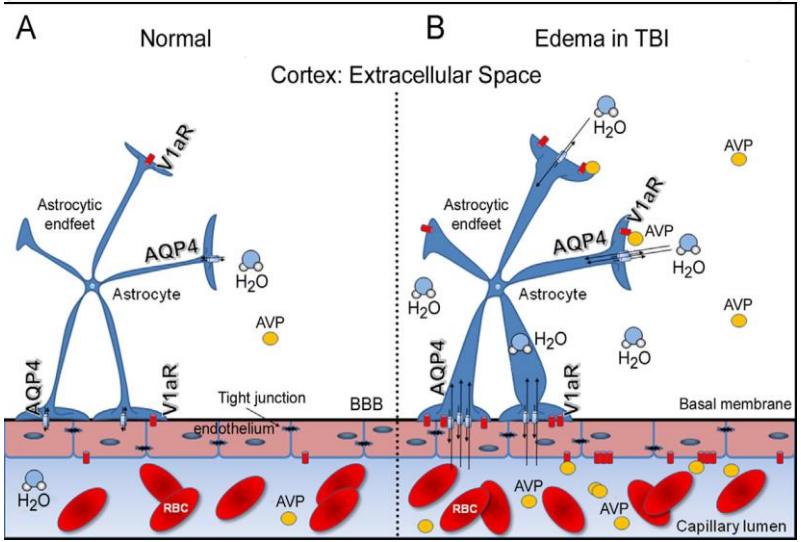
More than 530,000 U.S. Service Members have sustained traumatic brain injuries since 2000, with 82% classified “mild”

Over 55 million TBIs globally each year (90% mild)

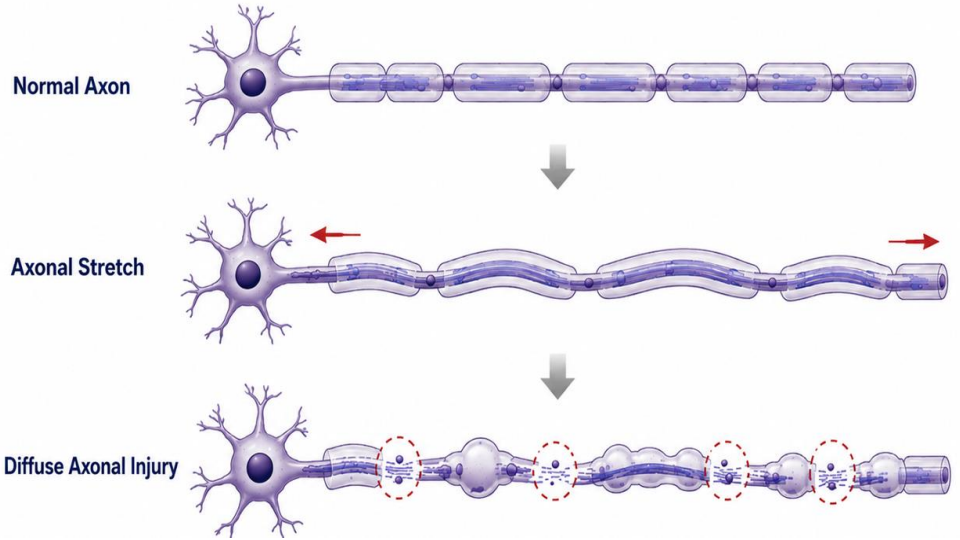
No approved injury-modifying drugs

Increased vasopressin (AVP) 1a receptor signaling triggers the "secondary injury cascade" after TBI

- Head injury elevates brain AVP
- Increased V1a receptor activation dysregulates AQP4 and drives edema



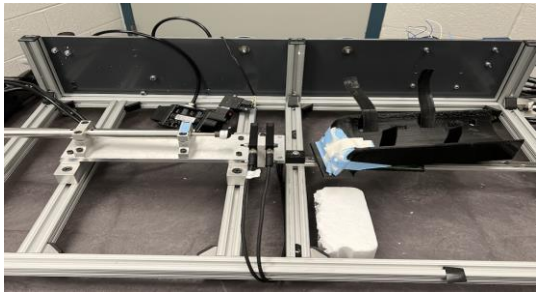
- Linear and rotational acceleration produce stretch and shear
- Disrupted cytoskeleton and neuronal injury



V1a antagonism reduces cellular injury and prevents cognitive deficits

Test AVNX102 and AVNX103: Orally bioavailable, highly selective, highly specific vasopressin 1a antagonists

Injury Model: single and repetitive (3) mild TBI in female and male rats induced using momentum exchange



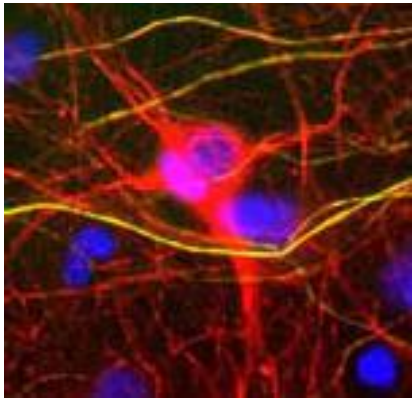
Treatment: 10 mg/kg ip 15 min and 18 hrs after each head impact

Determine drug effects on

-- Injury biomarkers: cerebral edema 6 and 48 hrs after insult and plasma Neurofilament Light Chain (NfL) over 14 days

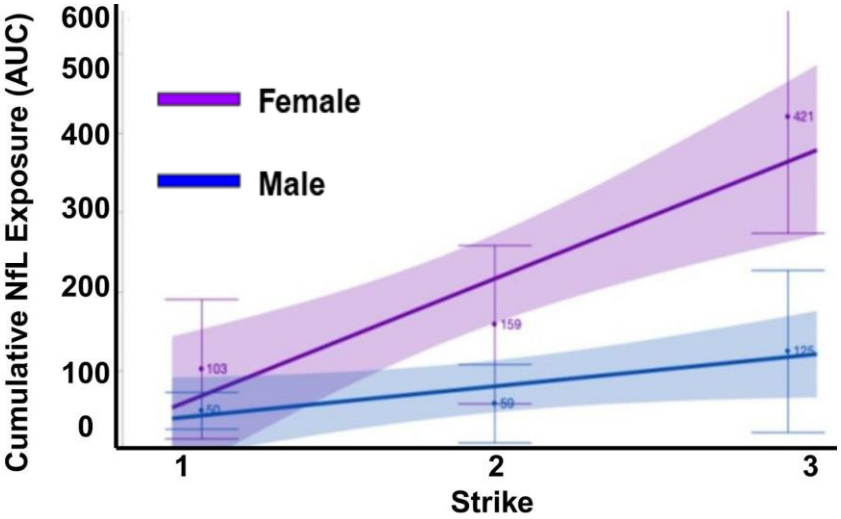
-- Memory with Novel Object Recognition Test

-- Circadian Rhythm using 24 hr activity over 5 days

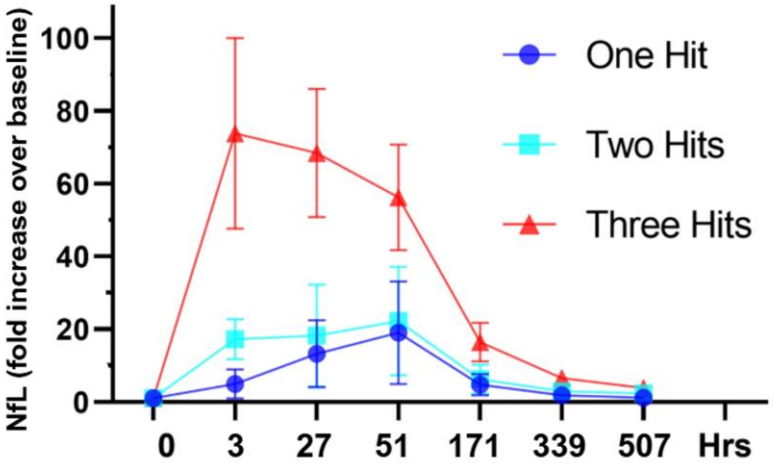


Objective: Identify lead candidate for development

rmTBI leads to more severe neuronal damage with a larger effect in females

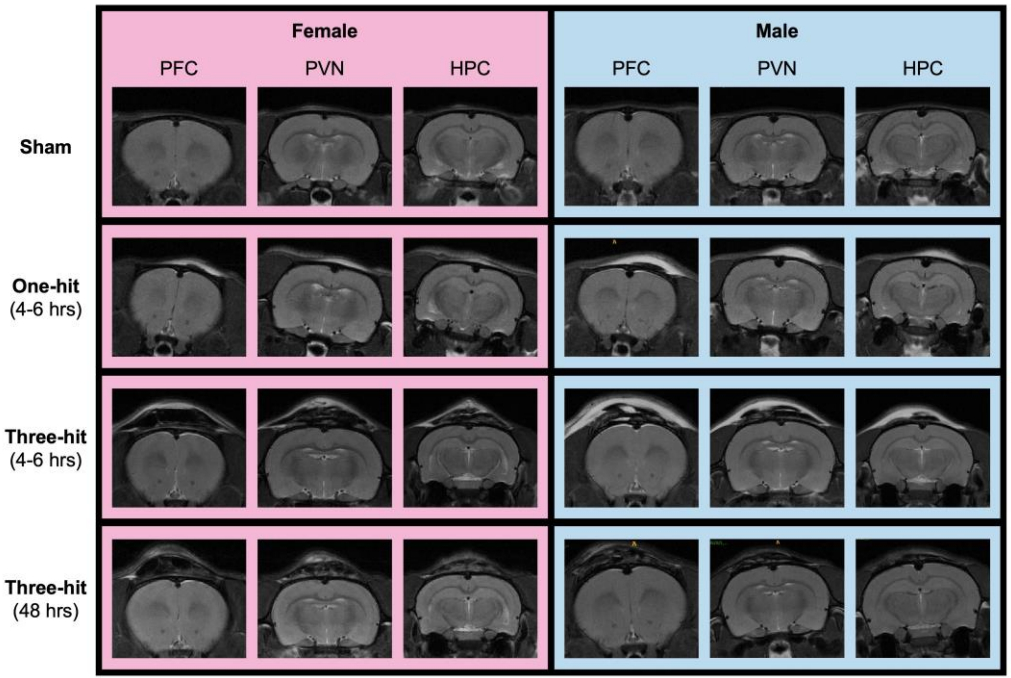


Total NfL exposure (AUC) after 1, 2 or 3 mild TBIs in female and male rats.



NfL levels (proportional increase vs baseline) after 1, 2 or 3 mild TBIs over 21 days (507 hrs) in female rats.

…without evidence of cerebral edema

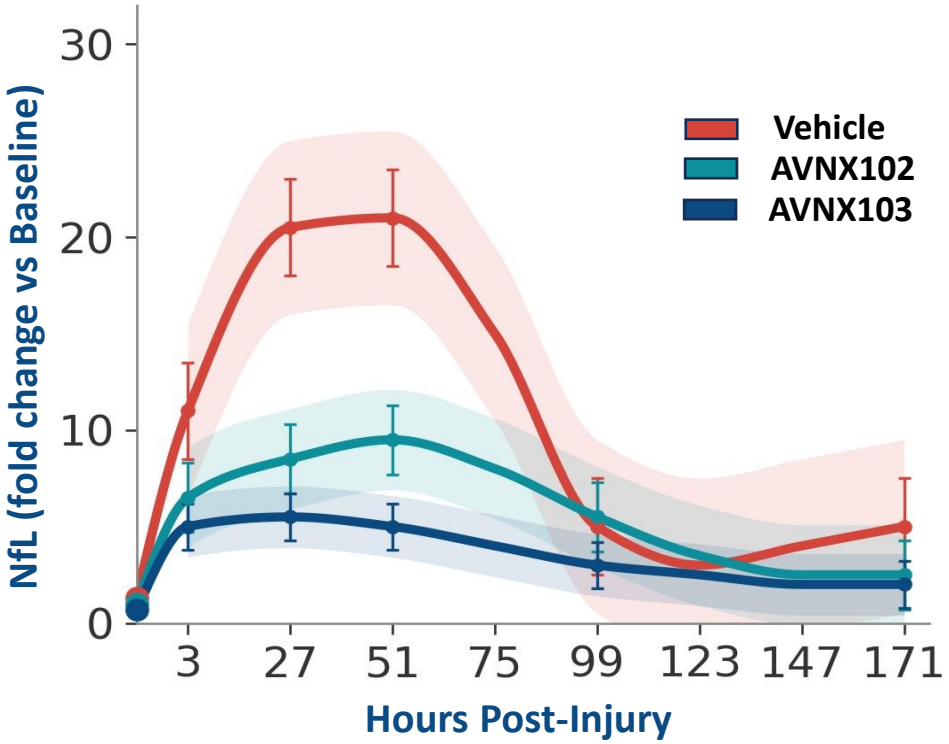


Key Findings

- Cerebral edema was not observed in either the 1 or 3 head strike conditions 4-6 hrs post injury
- In the rmTBI model, a second scan 48 hrs after the 3rd head strike also failed to detect edema
- No sex differences

NfL may be a more sensitive marker

AVNX102 and AVNX103 significantly reduce neuronal damage and death based on plasma NfL after rmTBI

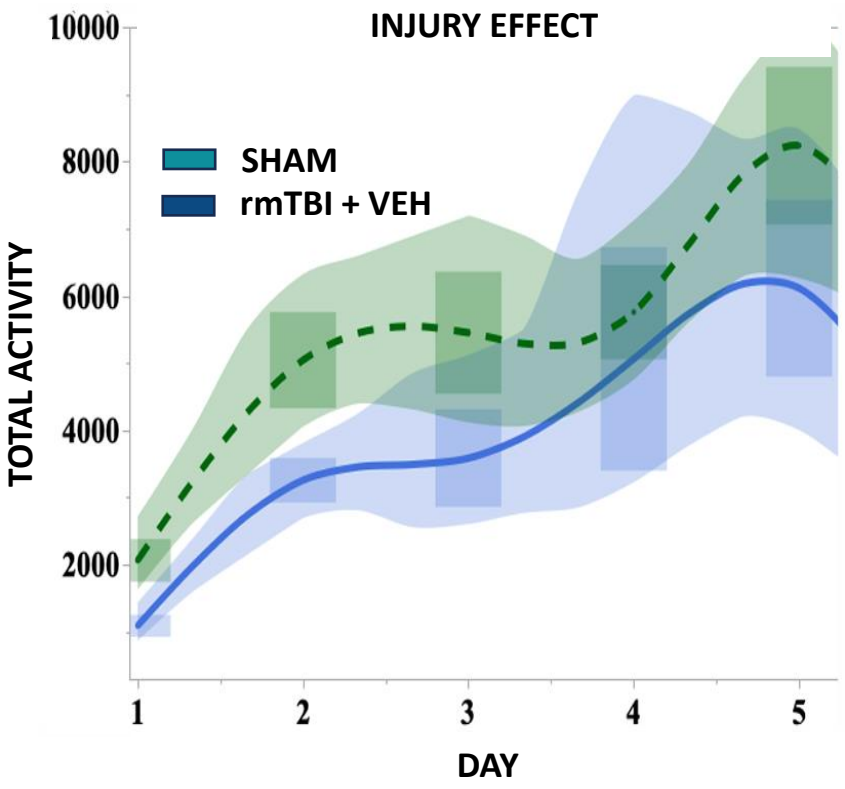


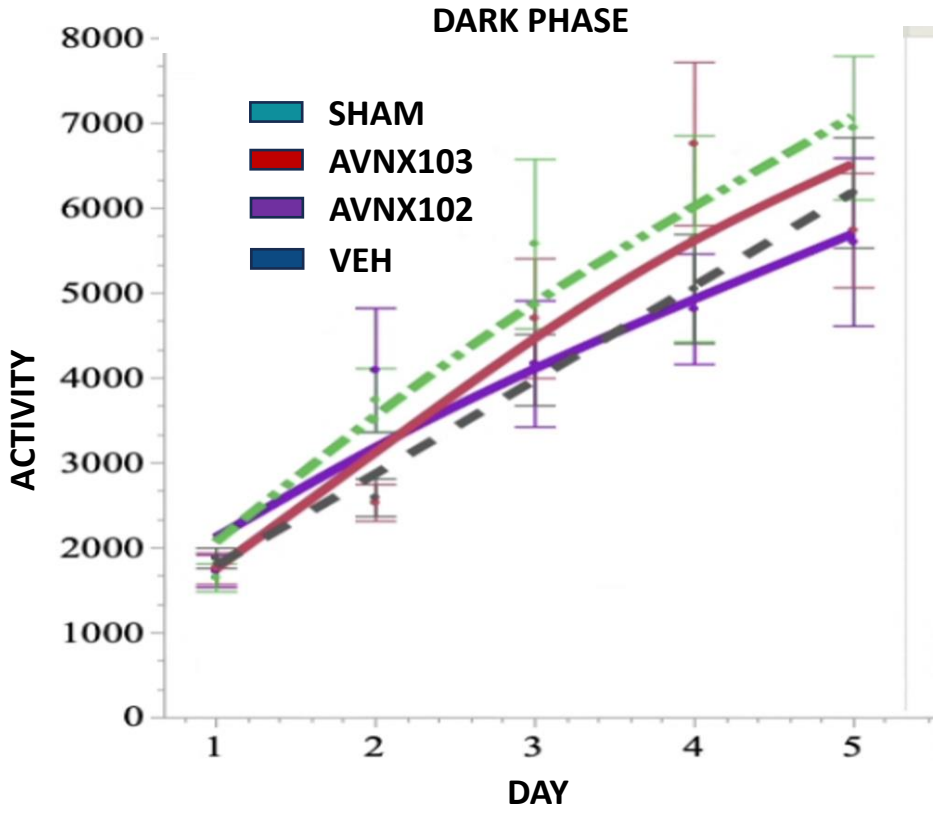
Key Findings

- NfL is significantly elevated in plasma from 3-99 hrs
- Both drug candidates effectively reduced plasma NfL
- AVNX103 was the more effective compound

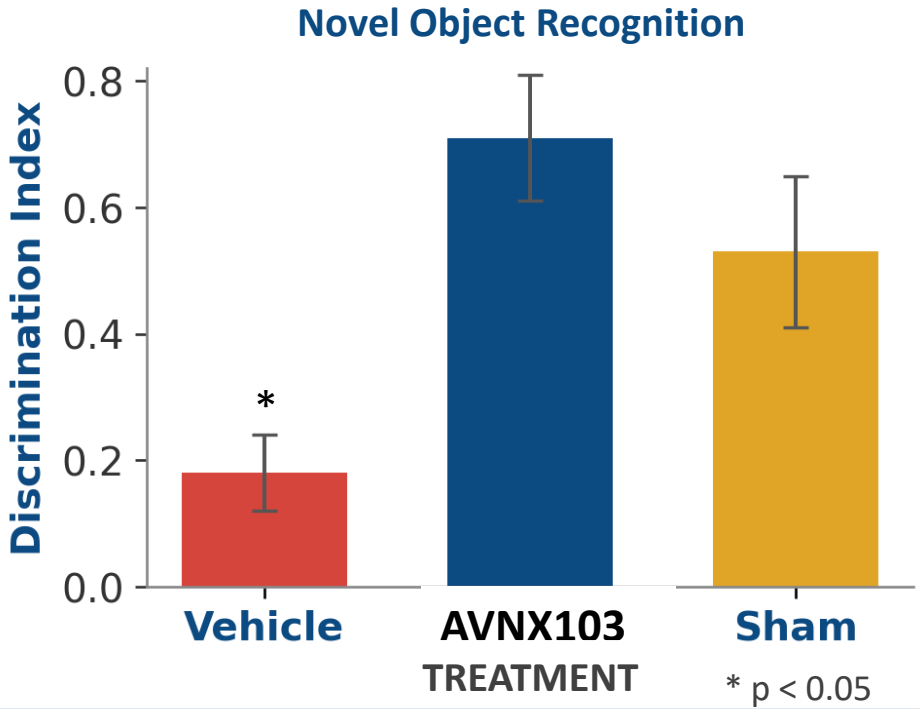
V1a antagonists reduce injury severity

AVNX103 normalizes circadian activity patterns in females





AVNX103 prevents cognitive decline on the NOR test 48 hours after rmTBI in females



Key Findings

- rmTBI + vehicle animals exhibited performance deficits compared to uninjured SHAM
- AVNX103 treatment prevented the deficit

Conclusions and Next Steps

V1aR antagonists show significant potential to reduce neuronal injury, restore circadian rhythms, and prevent cognitive decline following rmTBI

AVNX103 demonstrated greater and faster efficacy across tests, consistent with improved PK compared to prior generation compounds already in clinical studies. These results support its selection for development as a lead candidate

The use of sensitive blood-based biomarkers and functional assays supports clinical translation

Implement IND-enabling studies with AVNX103 in conjunction with additional physiological and cognitive endpoint investigations

Previous generation V1a antagonists demonstrated a strong safety profile in preclinical and clinical studies, suggesting that AVNX103 will be safe for human use

ACKNOWLEDGEMENTS

AT AZEVAN: M. Brownstein, S. Lu, H. Maibach, E. Damiano, D. Itzkowitz, C. Guillon, N. Heindel

OTHER COLLABORATORS: C. Ferris. E. Brengel, P. Kulkarni (Northeastern University); H. Dailey, M. Cordova, I. Faasuamalie, E. Farley, A. Wu, A. Marwaha (Lehigh University)

ADDITIONAL FINANCIAL SUPPORT: NIH; Azevan Pharmaceuticals, Inc. provided the test compounds

Thank You for Your Time and Attention!

For additional information:

Neal G. Simon, Ph.D.

Chief Executive Officer

ngsimon@azevan.com · 610-509-6127

www.azevan.com