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Tumor-Derived HAVCR1 As a Reliable Fluid Biomarker for the Diagnosis of CNS Lymphoma

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Guest: Dr. Shengjie Li is a Professor and Vice Chair for Academic Affairs in the Department of Clinical Laboratory at the Eye & ENT Hospital of Fudan University, Shanghai, China.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

Primary vitreoretinal lymphoma, or PVRL, is a rare form of lymphoma confined to the eyes that presents with relatively nonspecific symptoms, blurry vision, floaters, and painless vision loss. Because of this nonspecificity, PVRL is often misidentified as uveitis or other more common eye conditions and may take up to two years from the initial onset of symptoms to arrive at the correct diagnosis.

These delays have a huge negative impact on patient quality of life as 60 to 90% of PVRL cases spread from the eyes and develop into intracranial primary CNS lymphoma. Even when PVRL is suspected, currently available diagnostic tools often fail. Vitreous cytology only has a sensitivity of 45% and the IL-10/IL-6 ratio only has a diagnostic accuracy of 80 to 90%.

A new research article in the August 2026 issue of *Clinical Chemistry* presents the culmination of extensive efforts to find a better diagnostic tool. Using vitreous fluid, aqueous humor, and cerebrospinal fluid, the authors identified a new biomarker with an area under the curve [AUC] of 0.95 in a population-based analysis showing its value as a potential screening tool. Further, the biomarker concentrations dropped dramatically following complete remission confirming the marker is a true indicator of disease rather than an artifact of the discovery process.

Today, we're joined by the article's lead author. Dr. Shengjie Li is a Professor and Vice Chair for Academic Affairs in the Department of Clinical Laboratory at the Eye and ENT Hospital of Fudan University, Shanghai, China.

So, Dr. Li, what motivated your team to search for a new fluid biomarker for primary vitreoretinal lymphoma and what unmet clinical challenges were you trying to overcome?

Shengjie Li: Thank you for this important question. Primary central nervous system lymphoma, or PCNSL, is a rare but highly aggressive lymphoma that is restricted to immune-privileged sites including the brain, spinal cord, and eyes. Primary vitreoretinal lymphoma, or PVRL, represents an ocular manifestation of PCNSL and can involve the retina, vitreous, and other intraocular structures.

Although PCNSL accounts for only a small proportion of lymphomas, it is clinically important because of its aggressive behavior and the severe consequences of delayed diagnosis. In particular, PVRL is extremely challenging because its early manifestation often mimics common inflammatory eye diseases, especially uveitis. As a result, many patients experience prolonged diagnostic delays and may receive repeated anti-inflammatory treatments before the correct diagnosis is established.

The current diagnostic approaches also have important limitations. Vitreous biopsy and cytological examination remain important diagnostic methods but lymphoma cells in ocular fluids are often scarce and fragile, which reduces diagnostic sensitivity. This challenge is particularly significant after corticosteroid exposure when tumor cells may become even more difficult to detect. Molecular approaches such as *MYD88* mutation testing have improved diagnostic accuracy but they also depend on obtaining sufficient tumor-derived material.

From a clinical laboratory perspective, we wanted to answer an important question: Could we identify a tumor-derived molecule that can be detected in accessible body fluids and provide a reliable signal of lymphoma presence? Therefore, our goal was not simply to discover another inflammatory marker. Instead, we aimed to identify a biomarker that directly reflects tumor biology and could support earlier diagnosis through minimally invasive sampling.

To achieve this, we designed a multicohort study integrating unbiased proteomic discovery, independent validation and biological characterization. Ultimately, we identified HAVCR1 as a tumor-derived fluid biomarker with potential clinical value for both diagnosis and monitoring of CNS lymphoma.

Bob Barrett: Doctor, HAVCR1 was identified through large-scale proteomic profiling as the most consistent biomarker candidate. How did your discovery strategy lead to this finding and why did you focus on ocular fluid and cerebrospinal fluid rather than blood?

Shengjie Li: The discovery strategy was designed to overcome the limitations of traditional candidate-based biomarker approaches. We first performed large-scale proteomic

profiling using Olink platforms, analyzing more than 1,000 proteins in ocular fluids including aqueous humor and vitreous fluid from patients with PVRL, and different control groups including normal individuals and patients with uveitis.

An important consideration in our study design was the selection of biological samples. Although blood is the most commonly used clinical specimen, CNS lymphoma occurs in immune-privileged compartments and the tumor-derived signals may be diluted or difficult to detect in the peripheral circulation.

In contrast, ocular fluids and cerebrospinal fluid are anatomically closer to the tumor sites. These fluids may contain enriched tumor-derived molecules allowing more direct detection of lymphoma-associated signals. For PVRL, aqueous humor has additional advantages because it can be collected through a relatively simple and minimally invasive procedure compared with vitreous biopsy. For PCNSL, cerebrospinal fluid provides a direct window into the CNS microenvironment.

Therefore, we hypothesized that local biofluids might provide greater sensitivity and specificity for detecting CNS lymphoma compared with systemic blood samples. Using this strategy, HAVCR1 emerged as the only protein consistently elevated in PVRL patients compared with both normal controls and uveitis controls across multiple independent comparisons.

We then performed independent validation using additional patient cohorts and different detector methods. HAVCR1 demonstrated excellent diagnostic performance in aqueous humor including an AUC of 0.997 in an independent validation cohort. Furthermore, in cerebrospinal fluid from patients with PCNSL, HAVCR1 also showed very high diagnostic accuracy with AUC values approaching 1.0.

What makes HAVCR1 different from previous biomarkers is its biological origin. Many existing biomarkers such as IL-10 mainly reflect inflammatory changes within the tumor microenvironment. However, inflammation can occur in many ocular and neurological diseases. In contrast, our single nucleus RNA sequencing and immunohistochemistry analyses demonstrated that HAVCR1 is predominantly expressed by malignant lymphoma cells rather than surrounding immune or stromal cells. Therefore, HAVCR1 represents a tumor-derived biomarker, which may explain its high specificity for CNS lymphoma.

Bob Barrett: Well, your study demonstrated excellent diagnostic performance of HAVCR1 in aqueous humor and cerebrospinal

fluid. How could HAVCR1 potentially change the clinical workflow for diagnosing CNS lymphoma?

Shengjie Li: We believe HAVCR1 has the potential to complement and improve current diagnostic workflows rather than immediately replace existing approaches. Currently, diagnosing PVRL requires integration of multiple methods including ophthalmic examination, imaging, vitreous cytology, molecular testing, and cytokine analysis. However, each approach has limitations. For example, vitreous biopsy is invasive and may still produce inconclusive results because lymphoma cells are often present at very low abundance. In addition, inflammatory diseases such as uveitis can produce similar clinical manifestations creating significant diagnostic uncertainty.

Our study suggests that HAVCR1 measurement in ocular fluids, particularly aqueous humor, may provide a minimally invasive approach for identifying patients at high risk of lymphoma. Importantly, we validated HAVCR1 not only in retrospective discovery and validation cohorts but also in large hospital-based and population-based screening settings supporting its potential clinical applicability.

Another important finding was that HAVCR1 levels decreased significantly after successful treatment. This indicates that HAVCR1 may have value not only for initial diagnosis but also for monitoring treatment, response and potentially detecting disease activity over time. In the future, we envision HAVCR1 being incorporated into a comprehensive diagnostic strategy together with imaging, cytokine measurements such as IL-10, and molecular testing such as *MYD88* mutation analysis. The ultimate goal is to reduce diagnostic delays, minimize unnecessary invasive procedures, and allow earlier initiation of appropriate therapy.

Bob Barrett: Well, finally, Dr. Li, what are the remaining challenges before HAVCR1 can become part of the routine clinical practice and what are the next directions for your research?

Shengjie Li: Although our findings are encouraging, several important steps remain before HAVCR1 can be widely implemented in clinical practice. First, larger prospective studies are needed to validate HAVCR1 performance across different healthcare systems and diverse patient populations. Although we perform the validation across multiple cohorts including large hospital-based and population-based settings, international validation will be important to confirm generalizability.

Second, standardization will be critical. Clinical implementation requires standardized detection platforms, quality control procedures, reference ranges, and clearly defined clinical thresholds.

Third, larger longitudinal studies are needed to better understand HAVCR1 dynamics during different disease stages including diagnosis, remission and potential relapse.

Looking forward, we are particularly interested in developing integrated precision diagnostic strategies seeing as lymphoma is biologically heterogeneous and a single biomarker may not capture all aspects of disease biology. Therefore, combining HAVCR1 with molecular markers such as *MYD88* mutation status, cytokine profiles, imaging characteristics, and artificial intelligence-based clinical prediction models may provide a more comprehensive diagnostic framework.

Ultimately, our goal is to transform CNS lymphoma diagnosis from a biopsy-dependent approach toward a minimally invasive biomarker-guided strategy that enables earlier detection, better monitoring, and more personalized patient management.

Bob Barrett: That was Dr. Shengjie Li from Fudan University in Shanghai, China. He wrote a research article in the August 2026 issue of *Clinical Chemistry* describing a new fluid biomarker for the diagnosis of CNS lymphoma, and he's been our guest in this podcast on that topic.

I'm Bob Barrett. Thanks for listening.