

# Simultaneous infection by 2 viruses the key to studying rare lymphoma

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New research has found that a rare blood cancer can be simulated in the lab only by simultaneously infecting white blood cells with two viruses typically found in the tumors.

The successful creation of stable, [cancer](#)-like cells in the lab opens up opportunities for understanding the progression of this and related cancers and, perhaps, developing treatments.

Primary effusion lymphoma, PEL, is a rare blood cancer that primarily affects those with compromised immune systems, such as people infected with HIV. It is aggressive, and patients typically live just six months after being diagnosed.

The cancerous B cells that make up PEL nearly always harbor two [viruses](#), Epstein-Barr Virus, or EBV, and Kaposi's sarcoma-associated herpesvirus, or KSHV, which are both known to induce other types of cancer. Previous research has largely failed to stably infect B cells with both viruses in the lab, the key to developing a productive model of the cancer for further research.

University of Wisconsin-Madison professor of oncology Bill Sugden and his lab report this week in the *Proceedings of the National Academy of Sciences* that the two viruses support one another. When healthy B cells are exposed to both viruses within a day of one another, a small fraction of the cells remains infected for months.

In their work, the researchers discovered a rare population of EBV- and KSHV-infected cells that outcompeted other cells in the lab, behaving much like cells from PEL tumors. This population of quickly growing cells will help researchers untangle how this rare cancer forms in the body and how viruses can trigger cells to grow uncontrollably.

"All of a sudden we now have a tool to understand for the first time: how does a lymphoma possibly arise from [infection](#) of two tumor viruses and what are those two viruses contributing?" says Sugden, a member of the McArdle Laboratory for Cancer Research at the UW-Madison School of Medicine and Public Health.

In the past, researchers had tried to induce PEL-like behavior in B cells by infecting them with KSHV, the principal marker of the cancer. But those infections failed. Cells would slough off KSHV after days or

weeks and did not continue to grow.

For Sugden, who has long studied EBV—a herpes [virus](#) that is the cause of the common infection mononucleosis and of several cancers—the solution made sense: use the viruses together. After all, they're typically found together in cancer cells isolated from patients.

"Everything I know about this virus says that it will not be retained in these lymphomas unless it was doing something to contribute," says Sugden.

In early attempts, Aurélie Faure, who recently received her doctorate in Sugden's lab, found KSHV better infected B cells when they were activated by inflammatory chemicals to start dividing. Still, the infections were transient.

Because EBV infection also strongly activates B cells, Faure and Sugden reasoned the virus might promote infection by KSHV. So Faure introduced both viruses to the cells, staggering infection by one or more days. EBV greatly increased the fraction of B cells that were infected with KSHV, although it was still limited to about 2 percent of the original population.

Most importantly, EBV allowed the cells to grow and maintain the KSHV virus stably for months. Faure found that KSHV infection was most successful when cells were infected with EBV one day before being exposed to KSHV. That narrow window for success is likely one reason that dual infection and subsequent development into PEL is rare in people.

While the small fraction of doubly infected B cells was often overgrown by the larger population of partially infected cells, the researchers discovered one population that could hold its own. What they termed the

"fast" group of cells overgrew all others in the experiment, acting in many ways like the aggressive PEL cancer. Mitch Hayes, working with Faure and Sugden, found the cells had a form of antibody associated with PEL cells and shared patterns of gene expression in common with PEL tumors.

In all, the fast-growing population Sugden's lab developed appeared to be the first good model of PEL in the lab.

"Now we can go back with these cells and try to understand: What's the expression of EBV genes? What's the expression of KSHV genes in them that allow the cells to proliferate? What's the expression of EBV genes that allows KSHV be retained and vice versa?" says Sugden. Sugden is intent on teaching other cancer researchers how to produce this useful population of growing, stably and doubly infected cells. He is also offering up the original lines of cells his lab uncovered. That community resource will drive a better understanding of how these viruses manipulate [cells](#) to form a lethal cancer. "I'm going to do anything I possibly can to build on this work so that we attract other people to work on it," says Sugden.

**More information:** Aurélie Faure et al., "How Kaposi's sarcoma-associated herpesvirus stably transforms peripheral B cells towards lymphomagenesis," *PNAS* (2019).

[www.pnas.org/cgi/doi/10.1073/pnas.1905025116](http://www.pnas.org/cgi/doi/10.1073/pnas.1905025116)

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