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Misidentified and contaminated cell lines lead to faulty cancer science

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Modern cancer therapies start in cells – researchers compare cancer samples to healthy cells to discover how cancer is genetically different, and use cell lines to test promising new drugs. However, a University of Colorado Cancer Center study published this week in the journal *Gynecologic Oncology* shows that due to a high rate of contamination, misidentification and redundancy in widely available cell lines, researchers may be drawing faulty conclusions.

"I've seen faculty and graduate students leave my lab in tears when we discovered the cells on the label weren't the cells they were actually experimenting on," says Christopher Korch, PhD, investigator at the CU Cancer Center and director of the center's DNA Sequencing and Analysis Service, the paper's co-first author. "When you get a cell line, you have to look that gift horse in the mouth – there's up to a 40 percent chance it's a Trojan horse, not what it says it is."

For example, the cell line known as HES has been widely used as a "normal" model of endometrial cells since its development in 1989. There are literally hundreds of papers that, for example, look for differences between endometrial cancer cells and these supposedly normal HES endometrial cells. Unfortunately, HES is not, in fact, an endometrial cell line. It's another cell line known as HeLa which was first derived from cervical cancer.

"In the past, the technology to check cell lines didn't exist and so you can't really blame past researchers. But today it's cheap, it's easy and the

technology is widely available. There's no excuse to experiment on cells without first discovering what you're experimenting on. We've suggested that journals start requiring verification of cell lines as a prerequisite of publishing," says Andrew Bradford, PhD, CU Cancer Center investigator and associate professor in the CU School of Medicine Department of Obstetrics and Gynecology, the paper's senior author.

"In fact, the process of double-checking a cell line is the same process that Scotland Yard uses to identify murderers based on DNA evidence," says Monique Spillman, MD, PD, CU Cancer Center investigator and assistant professor in the CU School of Medicine Department of Obstetrics and Gynecology, the paper's co-first author. Here's how it works: You have a sample that you know is endometrial cells from a specific patient and you have a sample that purports to be (but may or may not be!) endometrial cells – is there a match? If so, you've convicted the suspect cell line. If not, as the team so often found, just as DNA mismatch has exonerated death row inmates, DNA mismatch showing that a cell line doesn't match it's label can call into question perhaps decades worth of research done using the cells.

While a misidentified cell line seems likely due to a SNAFU on the part of a lab assistant with a faulty filing system, there are more ways than clerical error to end up with the wrong label on a sample of cells.

"I see two people working with different cultures in the same hood, or using the same growth medium for the same cultures with the same pipette," Korch says. "And especially HeLa is superwoman – it can fly." HeLa cells can travel in aerosols and once they land where they shouldn't, they're so adaptive and aggressive that they tend to out compete other cell lines wherever they land – contamination leads to a quick HeLa takeover and perhaps a vial labeled HES when in fact it's HeLa.

"If you're going to make conclusions about endometrial cancer based on a cervical cancer line, your results are going to be flawed. It's not the same genetic pathways," Spillman says.

With his tongue only somewhat in his cheek, Korch reiterates Spillman's point, saying, "If you're studying prostate cancer with a cervical cancer cell line, you're going to have problems because men with prostates don't tend to have cervixes."

The work of Korch, Bradford, Spillman and colleagues including Twila Jackson builds on earlier work at the CU Cancer Center by investigators Rebecca Schweppe and Bryan Haugen who found 50 percent misidentification or contamination in available thyroid cell lines – for example, two were melanoma lines and another was a colon cancer line. The recent research finds the same systemic problems with cell lines of widely varying types.

"When you bring new cells into the lab, you need to work meticulously and carefully," says Korch. "You need to put them into quarantine until you know what they are."

Korch is working to put the group's data online, both allowing investigators elsewhere to compare their cell lines to the group's controls, and also to help research groups discover what, if not as labeled, some of the cell lines they tested might be. Again like criminal DNA evidence, it's all about building a database large enough to include a match.

Until then, "People really need to check their cells," says Bradford. "It's just that simple."

Provided by University of Colorado Denver