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First use in patient of conditionally reprogrammed cells delivers clinical response

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Using a newly discovered cell technology, Georgetown University Medical Center researchers were able to identify an effective therapy for a patient with a rare type of lung tumor. The single case study, reported in the September 27 issue of *New England Journal of Medicine*, provides a snapshot of the new technology's promising potential; however, researchers strongly caution that it could be years before validation studies are completed and regulatory approval received for its broader use.

The patient in the case study was a 24-year-old man with a 20 year history of HPV-positive recurrent respiratory papillomatosis (RRP). RRP is the most common benign neoplasm of the larynx usually due to infection by HPV that is acquired at birth during passage through an HPV-infected birth canal. The standard treatment is surgical removal of the tumors to clear the airway. The patient has had 350 such surgeries and has received chemotherapy for much of his life. In rare instances (three to five percent of cases), RRP can extend below the vocal cords. This patient's clinical course is even more uncommon because it spread into his lungs, a stage which occurs in less than one percent of people infected. There are no effective treatments for this disease stage, which is almost invariably fatal.

"Early on, we recognized this highly unusual case as one that would allow us to try the new technique with the added bonus of potentially helping the patient," explains the study's senior investigator, Richard Schlegel, M.D., Ph.D., chairman of the Department of Pathology at

Georgetown Lombardi Comprehensive Cancer Center, a part of Georgetown University Medical Center.

The technology used is one that keeps normal and tumor cells alive indefinitely in the laboratory—which previously had not been possible. In this case, the technique allowed researchers to establish live cultures of the patient's normal and tumor cells (with the patient's consent) so that treatments could be screened for in vitro activity. Within two weeks, the man's cells had rapidly generated to create stable cell cultures allowing Schlegel and his team to screen available drugs approved by the U.S. Food and Drug (FDA) for other uses.

"The patient's disease was rapidly progressing and he had no other treatment options," explains Schlegel. "Before he was asked to participate in this experiment, the patient was planning to enroll in a clinical trial with cidofovir, a drug frequently used to treat RRP, though without proven efficacy when the lungs are involved. The drugs chosen to be screened had shown some activity against certain HPV types."

One of the drugs tested on the patient's living cells was cidofovir, the drug the patient was to receive in the clinical trial. The cidofovir was ineffective in vitro. Another drug, which had been shown previously to be effective and selective against HPV cervical cancers, exhibited only moderate activity at high doses and did not discriminate between normal and tumor cells. A fourth drug, vorinostat (FDA-approved to treat cutaneous T-cell lymphoma), showed activity in vitro with selectivity for tumor cells versus normal cells.

"We talked to the patient and his doctors about what we observed and based on that, the patient was offered vironostat off-label," Schlegel says, explaining that the drug could be given "off-label" because it was FDA-approved for another indication. "We saw encouraging results after just three months with some tumor shrinkage and no new tumors. The

patient received the drug for one year resulting in stabilization of the tumors."

The technique used to propagate the normal and tumor cells was described recently in American Journal of Pathology (Feb. 2012). It relies on the use of Rho kinase (ROCK) inhibitor and fibroblast feeder cells. "In short, we discovered we can grow normal and tumor cells from the same patient forever, and nobody has been able to do that," Schlegel says. "Normal cell cultures for most organ systems can't be established in the lab, so it wasn't possible previously to compare normal and tumor cells directly."

The mechanisms by which these factors induce cell reprogramming and unlimited cell growth are currently under investigation, but efforts to validate this technique with other chemotherapy regimens are underway. Schlegel says teams of researchers from around the U.S. have visited his Georgetown lab to learn the "Georgetown Method," a phrase coined by researchers who provided an accompanying commentary at the time the work was published.

Schlegel says, "Our first clinical application utilizing this technique represents a powerful example of individualized medicine," but, he cautions, "It will take an army of researchers and solid science to figure out if this technique will be the advance we need to usher in a new era of personalized medicine."

Provided by Georgetown University Medical Center