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Therapeutic form of arsenic is a potential treatment for deadly type of brain cancer

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From Sherlock Holmes to Agatha Christie, arsenic is often the poison of choice in popular whodunits. But in ultra-low dosage, and in the right form, this naturally occurring chemical element can be a potent force against cancer.

Arsenic trioxide for years has been used to fend off a rare subtype of blood cancer known as acute promyelocytic leukemia (APL). Now, in a study led by Northwestern University Feinberg School of Medicine and the Translational Genomics Research Institute (TGen), this anti-cancer agent is being considered for use against glioblastoma multiforme (GBM), the most common and aggressive type of deadly brain tumors. The study was published today in *Molecular Cancer Research*, a journal of the American Association for Cancer Research (AACR).

"Our findings show that, for some patients, arsenic trioxide could be a powerful therapy that could extend the lives of certain glioblastoma patients by as much as three to four times the median expectation," said Dr. Harshil Dhruv, an Assistant Professor in TGen's Cancer and Cell Biology Division and one of the study's authors.

Median survival of glioblastoma patients is only 15 months, and survival statistics have improved only minimally over the past three decades. An estimated 17,000 Americans will die this year of brain and other nervous system cancers.

The origin of this new study had all the serendipitous turns of a good

mystery novel.

TGen had recently identified arsenic trioxide among a library of 650 compounds that could potentially be used against different subtypes of glioblastoma. While Dr. Dhruv was presenting these findings at a scientific conference, he met Dr. Jonathan Bell, who at the time was a graduate student in the Medical Scientist Training Program (MSTP) at Northwestern University. He described his work, showing resistance of a specific subtype of GBM against arsenic trioxide. In two clinical studies they examined, the therapeutic effects of arsenic trioxide were initially dismissed. But as Drs. Dhruv and Bell drilled down into the studies, they discovered that a specific subtype of GBM cells were more responsive to the arsenic trioxide treatment.

Northwestern was involved in one of the clinical trials, which tested the efficacy of arsenic trioxide in combination with temozolomide (TMZ) and radiation in treatment of GBM. Researchers at Northwestern were able to share biospecimens from their clinical trial with TGen.

"We were then able to identify these particular patients as having the same genomic signatures as those we had tentatively identified in our computer and laboratory screenings of potential therapies," Dr. Dhruv said.

The next step will be to validate the findings published in *Molecular Cancer Research* by initiating a new clinical trial specifically designed to match arsenic trioxide with glioblastoma patients that have a specific genomic signature, according to Dr. Michael Berens, a TGen Deputy Director and Professor in TGen's Cancer and Cell Biology Division, and one of the study's authors. These patients also would receive TMZ, which is the current standard-of-care drug given to GBM patients.

"This is an amazing convergence of complimentary thinking," Dr.

Berens said. "We tripped over a clinical partner who said, 'Oh, we've already done the (preliminary) clinical trial.' "

"We sought to identify compounds that specifically disrupt the growth of different GBM molecular subtypes," said Dr. Leonidas Platanias, Director of the Robert H. Lurie Comprehensive Cancer Center at Northwestern's Feinberg School of Medicine, and the study's senior author.

Researchers reassessed the earlier clinical trials and zeroed in on mesenchymal (MES) and proneural (PN) glioma subtypes, whose genomic signatures differ according to distinct underlying misbehaving genes.

"Arsenic trioxide was found to be the most potent compound in non-MES GBM cells. We found that PN GBM patients responded better to ATO (arsenic trioxide) than any other subtypes as demonstrated by longer overall and progression-free survival," said Dr. Bell, the study's lead author.

Researchers identified two additional advantages of using arsenic trioxide.

First, it is a small molecule able to penetrate the network of ultra-small capillaries—the blood-brain barrier—that surrounds the brain and spinal fluid and protects the central nervous system from most toxins and spikes in hormones. It is this barrier that prevents most other anti-cancer drugs from attacking brain tumors.

Second, its costs are minimal, since its source material, arsenic, is abundant in nature.

"Rather than treat all patients, we want to design a prospective clinical

trial that we can enrich for those patients whose genomic signatures indicate they would be the best candidates for success," Dr. Dhruv said. "This would be a biomarker-driven, precision-medicine clinical trial for glioblastoma—a way to match the right drug to the right patient."

More information: *Molecular Cancer Research* (2017). DOI: 10.1158/1541-7786.MCR-17-0397 , mcr.aacrjournals.org/content/e … 541-7786.MCR-17-0397

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