Brain tumor cells decimated by mitochondrial 'smart bomb'

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The new drug MP-MUS (yellow) attacks cancer cell mitochondria by infiltrating both inner and outer membranes (green) after being converted from an inactive, non-toxic form to an active, toxic form by the enzyme MAO-B (purple). Once inside, the drug damages mitochondrial DNA, which cannot be repaired. Credit: Dr. David Baskin laboratory, Houston Methodist Hospital

An experimental drug that attacks brain tumor tissue by crippling the cells' energy source called the mitochondria has passed early tests in animal models and human tissue cultures, say Houston Methodist scientists.

As reported on the cover of the April 2015 *ChemMedChem* (early online), Houston Methodist Kenneth R. Peak Brain & Pituitary Tumor Center Director David S. Baskin, M.D., and Peak Center Head of Research Martyn Sharpe, Ph.D. designed a drug called MP-MUS that destroyed 90 to 95 percent of malignant glioma cells, yet in other experiments did not seem to adversely affect healthy human brain cells (in vitro). This compliments a soon to be published extensive study showing the same drug can treat human brain cancer grown in the brains of mice. Researchers hope to begin testing the drug in human clinical trials in 2016 or 2017

"We are very optimistic that we'll get there," said Baskin, also Vice Chair of the Department of Neurosurgery at Houston Methodist Hospital. "Our past work has shown that MP-MUS has very low toxicity until it gets into tumor cells. Once it arrives, it is changed to its active form, doing a lot of damage where we want it to, leaving healthy brain cells alone—a bit like a 'smart bomb.' To our knowledge, this is the first known example of selective mitochondrial chemotherapy, which we believe represents a powerful new approach to brain cancer."

Medical options for brain tumor patients are woeful, Baskin said. "It's a horrible diagnosis. Because of where the tumors are located, and because of the way they can infiltrate healthy tissue, surgery is often not helpful long term. The most effective chemotherapy drug available right now, temozolomide, only extends life from 9 to 15 months, and patients' quality of life during that period isn't very good."

For that reason, Baskin said, he and researchers around the world have been looking for new treatment approaches, such as vaccines intended to aid the body's immune system's recognition and removal of tumor cells, gene therapy and, in the present case, targeting tumor cell mitochondria.

Gliomas (a type of brain tumor) develop from brain cells called astrocytes. Gliomas account for as much as 20 to 30 percent of all tumors of the brain and central nervous system.

Mitochondria are often referred to as the "powerhouses" of cells—including misbehaving cancer cells—because they help cells create energy. In cancer cells this feature is partially switched off, causing cells to rely on other systems that generate energy. The numerous pill-shaped mitochondria in each cell perform a number of other crucial functions, however, and even cancer cells cannot grow and divide without healthy mitochondria.

As luck would have it, an enzyme called MAO-B is over-expressed in brain tumor cells, which is the target of MP-MUS. This means that healthy cells are only exposed to low levels of MP-MUS and their mitochondria to very low levels of P+-MUS, Baskin says. On the other hand, in tumor cells the vast majority of the pro-drug is converted into P+-MUS, which essentially traps the drug inside their mitochondria where it attacks the mitochondrial DNA.

"We found that we could achieve profound effects with MP-MUS at very low concentrations, around 75 micromolar," said Baskin, Professor of Neurological Surgery, Weill Cornell Medical College. "By contrast, temozolomide must be used at concentrations two to three times that to be of any use to patients. Our approach is designed to capitalize on what is going inside the cells. Tumor cells have much more MAO-B, and when challenged, make even more MAO-B as a sort of defensive response. We hope that we are one step ahead of the cancer cells, as we

are using that very fact to kill them."

The researchers reported MP-MUS's toxicity to healthy cells remained low at concentrations as high as 180 micromolar. This information will be useful to the researchers as they consider safety and efficacy trials in human patients.

Houston Methodist and Baskin and Sharpe entered into an agreement with Virtici, LLC to develop MP-MUS and are currently preparing toxicology studies which are required prior to clinical trials.

Provided by Houston Methodist