July 28, 2022 03:14 PM EDTUpdated 04:29 PM

R&D

By exploiting the DNA repair system, Yale scientists want to crack chemotherapy resistant brain cancer

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In 2005, Roger Stupp published an article in NEJM, showing that adding temozolomide to radiotherapy extended brain cancer patients' survival time by 2 months. For a cancer in which median survival was usually less than a year, that was practice-changing.

Temozolomide would be added to the first line of chemotherapies for glioma patients, and its use alongside radiation would be termed "The Stupp Protocol."

However, a large number of patients were unresponsive to TMZ, and many who were responsive would go on to develop resistance to TMZ.

In a new study published in Science https://www.science.org/doi/10.1126/science.abn7570, Yale scientists describe an alternative drug to TMZ that may overcome that resistance problem. Led by Seth Herzon and Ranjit Bindra, they looked specifically at glioblastoma cells that are MGMT-deficient — a biomarker for cells that would respond better to TMZ initially, but develop resistance later on.

MGMT is a DNA repair protein. It works via a "suicide" mechanism, in which it takes away a methyl group from the damaged DNA, thereby fixing it, but inactivates itself as a result. On the other hand, once in the body, TMZ breaks down to become an alkylating agent, which means it adds alkyl groups (of which the simplest is a methyl group) to the DNA, thereby damaging the DNA.

(Last year, scientists discovered that TMZ, once thought to be exceedingly stable, is also highly explosive, apparently. It's tentatively classified as a Class 1 explosive, putting it in the same zone as dynamite.)

In healthy cells where MGMT works as it should, after TMZ is added, the cells' DNA repair systems readily correct the DNA lesions. But in MGMT-deficient tumors, those lesions build up, which triggers the cell's mismatch repair system. The MMR system recognizes the DNA is damaged, and causes the tumor cells to die.

However, the problem is that eventually mutations pop up in the MMR pathway itself, and the tumor recurs.

So Herzon and Bindra conceived an approach that would, like TMZ, damage the DNA in glioma cells, but do away with the resistance once mutations happen in the MMR pathway. In their paper, they describe one candidate, KL-50, which is what's known as an interstrand crosslinking (ICL) agent. Essentially, it slowly creates a link between the two strands of

DNA — slow enough that healthy cells can reverse it. But in cancer cells, the link proves to be toxic and causes the cell to die.

Herzon noted that ICL agents "in and of itself [are] not a novel finding — those types of molecules are well known in the literature, and have been used unsuccessfully for decades in the clinic. What's unique about our compound is that it is, in essence, a cell lines-specific crosslinking agent, so it only forms these interstrand crosslinks in an MGMT-deficient background."

But to healthy cells, "the molecule is essentially invisible," Herzon said.

In addition, by using the ICL mechanism, the drug isn't dependent on the cell's MMR system.

"We designed it in a way so that it would be impervious to resistance mutations that are common with glioma. One of those is mutations in mismatch repair. With temozolomide, mismatch repair mutations render the drug completely inactive," Bindra said. "But we specifically made these DNA modifiers in a way that they're impervious to that mutation. But they're still dependent on the loss of MGMT, so they still have that therapeutic index."

"It's really a new way to approach tumor cell resistance, and also again, to exploit the DNA repair defects," Bindra said.
Roger Reddel

However, for gliomas, which have historically been difficult to treat, the jury remains out on whether such a drug will work. "The new treatment looks very good in preclinical studies, especially with regard to overcoming the most common mechanism of resistance to TMZ, but clinical trials will be required to determine whether it is better," Roger Reddel of the University of Sydney told Endpoints News in an email.

"GBM is a difficult tumor for many reasons including the way it infiltrates surrounding brain tissue which means it is difficult to remove completely by surgery, and the extensive heterogeneity within individual tumors and between tumors of the same type. The new approach does not specifically address any of these issues, but has the potential advantage that it seeks to improve one of the few treatments that has proven effective," Reddel, who wrote an accompanying editorial on the study in Science, noted.

Bindra and Herzon, along with co-author Kingson Lin, have spun their discovery into Modifi Bio, which they launched from stealth today.

"As a physician scientist [who has] dedicated my clinical career and the last 10 years treating adult and pediatric brain tumors, I think there's a lot of room to move on biomarker-directed therapies, that have really been rigorously validated in vitro and in vivo to set them up for the greatest chance of success in the clinic," Bindra, who directs Yale's brain tumor center, said.

“We’ve seen so many failures — they say GBM is a graveyard for therapeutics, but I say, if you bring dead drugs to the graveyard, they’re not going to suddenly live,” Bindra said.

Their biotech, Modifi Bio, starts with $6.4 million in seed funding, which it says will support IND-enabling studies and enable it to build out the platform that discovered KL-50, which Bindra terms a ‘DNA modifier.’

Notably, Roger Stupp also sits on Modifi’s advisory board. Modifi, derived from the Spanish word ‘modificado’, hopes to be in Phase I trials by 2024, it said.

“The new approach is also noteworthy because the drug design principle it uses could be extended to other tumor types with different DNA repair deficiencies,” Reddel also noted.

Durham-based Chimerix is another biotech taking the biomarker-based approach to gliomas. It bought Oncoceutics last year, and is testing its candidate in recurrent gliomas with an H3 K27M mutation.

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