Drug developed for pancreatic cancer shows promise against most aggressive form of medulloblastoma

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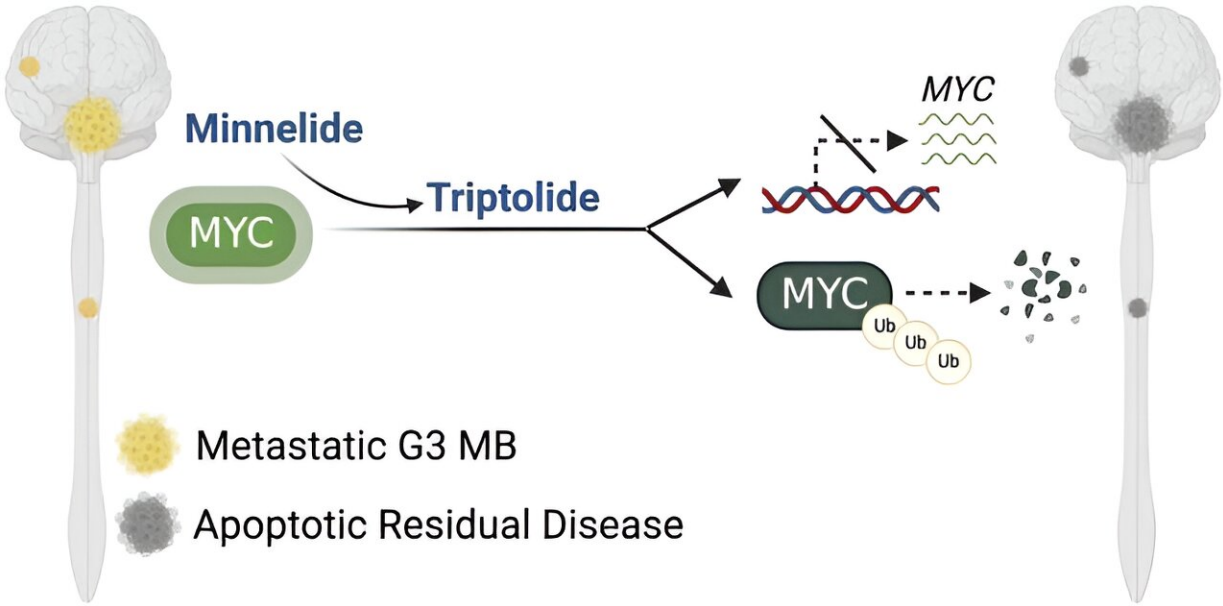

Graphical abstract. Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI171136

A drug that was developed to treat pancreatic cancer has now been shown to increase symptom-free survival in preclinical medulloblastoma models—all without showing signs of toxicity.

Medulloblastoma is the most common malignant brain tumor in children.

Survival rates vary according to which one of the four subtypes a patient has, but the worst survival rates, historically at about 40%, are for Group 3, which this research focused on.

Jezabel Rodriguez Blanco, Ph.D., an assistant professor who holds dual appointments at MUSC Hollings Cancer Center and the Darby Children's Research Institute at MUSC, led the research, published in the *Journal of Clinical Investigation.*

Her research focused on the drug triptolide, which is extracted from a vine used in traditional Chinese medicine, and its water-soluble prodrug version, Minnelide. A prodrug is an inactive medication that the body converts into an active drug through enzymatic or chemical reactions.

MYC is an oncogene, or gene that has the potential to cause cancer. MYC is dysregulated, or out of control, in about 70% of human cancers, and it shows up in much higher levels in Group 3 medulloblastoma than in the other medulloblastoma subgroups. Despite its well-known role in cancer, this oncogene historically has been considered impossible to target with drugs.

Despite its poor druggability, previous research in other cancers had shown that triptolide and its derivatives had the ability to target MYC. When Blanco was still a postdoctoral fellow at the University of Miami, her mentor, David Robbins, Ph.D., attended a presentation by the research team that showed that the more copies of MYC that a tumor has, the better that triptolide works.

"He came to me, and he told me, 'You know, as Group 3 medulloblastoma has many MYC copies, you should get some research models and try the drug,'" Blanco recalled. She started the project from scratch. "I started talking to people, getting cell lines and animal models, learning how to propagate them, getting the drug, using it."

Even as she started her faculty position at MUSC and began to focus most of her research on the Sonic Hedgehog subgroup of medulloblastoma, she continued to work on the Group 3 research as a side project. She knew how well triptolide was working in these hard-to-treat tumors, and she did not want her initial results to fall through the cracks.

Determining the mechanism of action has been the most challenging part of the project, she noted, due to the drug's multiple effects, and there could still be additional mechanisms beyond those that Blanco identified.

"It was affecting MYC gene expression by affecting the RNA pol II activity, and then it was affecting how long the protein lasts. So, the fact that it's working through two different mechanisms on this oncogene may explain why it's so effective in tumors that have extra copies of MYC," she said, explaining that RNA polymerase II is a protein that helps to make copies of DNA instructions, which are used to produce proteins in the cell.

Despite the challenges of narrowing down the mechanism of action specific to the cancer, it was quite clear that however it worked, it did work, she said.

The efficacy was 100-times higher in the Group 3 tumors with extra MYC copies than in the Sonic Hedgehog tumors with normal levels of MYC, she said. She found that Minnelide reduced tumor growth and the spread of cancer cells to the thin tissues that cover the brain and spinal cord, called leptomeninges. It also increased the efficacy of the chemotherapy drug cyclophosphamide, which is currently used in treatment.

Blanco decided to move forward with publication rather than waiting to write a manuscript that answered all possible questions. Knowing that

most parents whose children receive a Group 3 medulloblastoma diagnosis will lose their child in less than two years was the incentive she needed to push this work out.

"There was a point at which I could not hold these data anymore because it was working so well that it needed to go out," she said. "The preclinical models were showing such a nice efficacy that it was like, OK, I cannot keep on holding this work, digging deeper into the mechanism of action because the kids that have Group 3 medulloblastoma are dying while we are doing those experiments."

Minnelide has been tested or is currently in testing in Phase I and Phase II clinical trials of adults with different types of cancer, including pancreatic cancer, where it showed some efficacy.

Blanco is hopeful that, with this new research on Group 3 medulloblastoma, a clinical trial for children with this disease can be launched.

Her paper is dedicated to the memory of Insley Horn, a 9-year-old Charleston girl who succumbed to one of these aggressive brain tumors. Research, Blanco said, is the only tool we have to prevent the loss of lives like Insley's.

More information: Jezabel Rodriguez-Blanco et al, Triptolide and its prodrug Minnelide target high-risk MYC-amplified medulloblastoma in preclinical models, *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI171136

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